General

Guideline Title

Antithrombotic therapy supplement.

Bibliographic Source(s)

Maddali S, Biring T, Bluhm J, Kopecky S, Krueger K, Larson T, Mikelson M, Miley T, Morton C, Pruthi R, Schullo-Feulner A. Antithrombotic therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Feb. 88 p. [186 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Maddali S, Morton C, Biring T, Bluhm J, Hanson M, Kopecky S, Krueger K, Larson T, Mikelson M, Miley T, Pruthi R, Schullo-Feulner A. Antithrombotic therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2012 May. 87 p.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC) and the Institute for Clinical Systems Improvement (ICSI): For a description of what has changed since the previous version of this guidance, refer to Summary of Changes Report – February 2013 .

These recommendations supplement the recommendations on anticoagulation therapy provided in the NGC summaries of the ICSI guidelines: Heart failure in adults; Diagnosis and initial treatment of ischemic stroke; Diagnosis and treatment of chest pain and acute coronary syndrome (ACS); Venous Thromboembolism Diagnosis and Treatment; and Venous Thromboembolism Prophylaxis.

Class of evidence (A-D, M, R, X) ratings are defined at the end of the "Major Recommendations" field.

Clinical Highlights

- There are no circumstances under which patients absolutely should or should not receive anticoagulation therapy, with the exception of life-threatening bleeding. Clinicians must consider the risks and benefits of anticoagulation therapy for a patient based upon the individual's risk for thrombosis if not treated weighed against the risk of bleeding if treated. (*Introduction, Annotations #1.0, 1.1, 1.2, 1.4, 1.6, 2.1, 2.2, 2.3, 2.4, 2.82, 3.2, 3.3, 3.4, 3.8, 4.0a, 4.1a, 4.1b, 4.2a, 4.2b, 4.3a, 4.3b, 4.4b, 4.8a, 4.8b, 5.0, 5.1, 5.2, 5.3, 5.4b, 5.8, 6.1b, 6.2a, 6.2b, 6.3a, 6.3b, 6.4b*)
- In the initial phase of treatment for patients with active thrombosis (such as acute deep vein thrombosis [DVT]) or high risk of thrombosis, immediate-acting anticoagulant agents (unfractionated heparin [UFH]/low-molecular-weight heparin [LMWH]/fondaparinux) should be used

concomitant with warfarin. (*Annotation #1.6*)

- Loading doses of warfarin should be avoided. (*Annotation #1.6*)
- Many prescription medications or over-the-counter remedies, including dietary supplements and herbs, may alter the effectiveness of warfarin or vitamin K antagonists (detected by the international normalized ratio [INR]) and/or reduce the effectiveness of platelets (not detected by the INR). (*Annotations #1.6*)
- Vitamin K may be used to reverse supratherapeutic anticoagulation with warfarin. The dose of vitamin K depends upon the degree of INR elevation and/or signs and symptoms of bleeding. Vitamin K can lead to warfarin resistance and subsequently to an increased risk of thromboembolism. (*Annotation #1.8*)
- Regardless of the anticoagulant used, it is important that patients know they must always inform their physician and other health care providers that they are on anticoagulation therapy, especially if they are undergoing an invasive procedure. (*Annotations #1.9, 3.9, 4.9a, 5.9*)
- Patients should be encouraged and empowered to play an active role in the self-management of their treatment. Self-management is best initiated and sustained through active involvement of patients and family members with their multidisciplinary health care team. This educational partnership should be encouraged to decrease potential risks and improve understanding of the importance of patient adherence to their treatment regimen. (*Annotation #1.9, 3.9, 4.9a, 4.9c, 5.9, 6.9a, 6.9b*)
- Recent concerns about concomitant use of proton pump inhibitors (PPI) and clopidogrel ought to be addressed on a patient-by-patient basis with discontinuation of PPI if there is no definite indication for its use; H2 blockers could be considered if acid-suppression is desired. (ICSI Antithrombotic work group consensus-based recommendation). (*Annotation #6.0a*)
- Dabigatran has been U.S. Food and Drug Administration (FDA) approved for use only in non-valvular atrial fibrillation as an alternative to warfarin for stroke prevention. (*Annotation #4.0*)
- Lepirudin was removed from the European market starting April 1, 2012, and will no longer be manufactured after May 2013. If the United States experiences absence of lepirudin, use argatroban or bivalirudin in patients with heparin-induced thrombocytopenia. (*Annotation #4.0b*).
- Rivaroxaban has been FDA approved for the prevention of DVT and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery, treatment of DVT and PE and for non-valvular atrial fibrillation for stroke prevention. (Annotation #5.0)

Algorithm Annotations

1. Warfarin
   1.0. Introduction, Warfarin

   Warfarin is used in the chronic management of patients with several types of thrombotic diseases. It produces its anticoagulant effect by inhibiting the vitamin K-dependent production of clotting factors II, VII, IX, and X, as well as the anticoagulant proteins C and S. The antithrombotic effect of warfarin is dependent on reduction of factor II (prothrombin), the factor with the longest half-life of 60 to 72 hours. Because of this, warfarin is not fully effective in the initial several days of therapy *[R]*.

   When determining the efficacy and tolerability of warfarin in patients with non-valvular atrial fibrillation, the clinical trials excluded patients using the following criteria:

   Table. Exclusion Criteria Used in Trials Evaluating the Efficacy and Tolerability of Anticoagulation in Patients with Non-Valvular Atrial Fibrillation

Active bleeding
Active peptic ulcer disease
Known coagulation defects
Thrombocytopenia (platelet less than 50,000/mm^3) or platelet dysfunction
Recent hemorrhagic stroke
Non-compliant or unreliable patients
Patient is psychologically or socially unsuitable
Dementia or severe cognitive impairment
History of falls (three within the previous year or recurrent, injurious falls)
Excessive alcohol intake
Uncontrolled hypertension (greater than 180/100 mm Hg)
Daily use of non-steroidal anti-inflammatory drugs (NSAIDs)
Planned invasive procedure or major surgery

[R]

The clinician will need to balance the potential increased risk in bleeding against the potential decreased risk of thromboembolism when evaluating warfarin therapy.

1.1. Adverse Effects, Warfarin

Key Points:

- The most common adverse effect of warfarin is bleeding. Risk factors for bleeding include patient-related and treatment-related factors.

Bleeding

Patients treated with usual doses of warfarin have a 2% to 4% risk per year of bleeding episodes requiring transfusion, and a 0.2% risk per year of fatal hemorrhage. Risk factors for bleeding include patient-related factors and treatment-related factors.

Patient-related factors include age, previous episodes of bleeding, anemia (hematocrit [HCT] less than 30%), hypertension, heart disease, cerebrovascular disease, renal disease, history of gastrointestinal (GI) hemorrhage, active peptic ulcer disease or liver disease, recent or imminent surgery, trauma, excessive alcohol intake, unreliability, frequent or significant falls, regular use of non-steroidal anti-inflammatory drugs (NSAIDs), and use of other medications or natural remedies.

The FDA recently approved updated labeling for warfarin. The agency reports that people with variations in two genes, CYP2C9 and VKORC1, are individually responsible for 35% to 50% of the variable dose response to warfarin *[R]*. These genetic variations affect the dose of warfarin that individual patients will need to achieve and maintain therapeutic INRs. This issue is discussed further under *Initiation of Warfarin* in Annotation #1.6, "Dosing, Warfarin."

Advanced patient age and hypertension are two predictors of risk strongly related to the inherent risk of intracerebral hemorrhage in patients not receiving anticoagulation *[R]*. Combined literature sources support age as a risk for intracerebral hemorrhage that increases by 1.85/year/decade, with particular caution above 75 years of age *[M]*, *[R]*.

Treatment-related factors include duration, intensity, and variability of warfarin treatment, concomitant use of aspirin, and support patients receive from their providers and home environments. Please refer to Appendix A, "Risk Factors for Thromboembolic Event," and Appendix B, "Risk Factors for Bleeding during Warfarin Therapy," in the original guideline document. For additional information on bleeding risk in anticoagulation therapy see http://circ.ahajournals.org/content/110/16/2287 .

Risk factors for bleeding should not be considered absolute contraindications to anticoagulant therapy. Some risk factors for bleeding (such as age) are also risk factors for thromboembolism. The potential increased risk of bleeding must be balanced against the potential decreased risk of thromboembolism.

[B], *[C]*, *[D]*, *[R]*

Skin Necrosis

Skin necrosis is a rare but serious complication of warfarin therapy that can occur in two situations: 1) in patients with acute heparin-induced thrombocytopenia (HIT), and 2) in patients with pre-existing congenital protein C or protein S deficiency.

1. HIT-associated skin necrosis: Generally occurs in patients who have active HIT when warfarin is prematurely initiated or initiated in high/loading doses.
2. Skin necrosis associated with congenital protein C/S deficiency (incidence 0.01% to 0.1%): Patients initiated on warfarin without heparin bridging may develop skin necrosis that typically occurs on the third to eighth day of therapy.

Patients present with painful localized skin lesions due to thrombosis of venules and capillaries within subcutaneous fat. These lesions may occur in areas of fatty tissue such as the breasts, abdomen, or even in extremities. Warfarin should be discontinued in patients with suspected skin necrosis. Direct thrombin inhibitors (DTIs) should be initiated or continued in patients with HIT. Warfarin has been successfully used in such cases by initiating very low doses while continuing heparin/DTI and gradually escalating the dose over several weeks to avoid an abrupt drop in protein C levels before coagulation factors levels are reduced *[D]*. Because of the extreme rarity of this complication, routine pretesting for congenital protein C and protein S deficiency in all individuals prior to initiation of oral anticoagulation is not advised *[D]*, *[R]*. However, if there is a strong family history of venous thromboembolism, such testing should be considered.

Purple Toe Syndrome

Purple toe syndrome and other manifestations of peripheral emboli may rarely complicate warfarin therapy, usually 3 to 10 weeks after initiation of therapy. Causes of purple toe syndrome other than warfarin should be considered when making a treatment decision. These include vasculitis, acute myocardial infarction (MI) with embolism, and diabetes mellitus *[D]*, *[R]*.

Less Serious Adverse Effects

Adverse effects that are less serious include alopecia, osteoporosis, gastrointestinal discomfort, and rash. Management of these adverse effects should be managed on an individual basis.

[B], *[D]*

1.2. Contraindications, Warfarin

Key Points:

- All contraindications are relative to a patient's risk for thrombosis weighed against the risk for bleeding while on anticoagulation therapy.

Warfarin Allergy or Intolerance

Acute rash, hepatitis, diarrhea or nausea may indicate an allergy or intolerance to warfarin.

Hemorrhage

Anticoagulation with warfarin is contraindicated in patients with active hemorrhage. The decision to initiate anticoagulation should be individualized for patients with a history of recent hemorrhage. Again, this is dependent on circumstances including the type of hemorrhage and the indication for anticoagulation. Withholding anticoagulation for 4 to 6 weeks may be prudent for non-central nervous system bleeds. This duration may be longer for central nervous system (CNS) bleeds and needs to be assessed on a case-by-case basis.

Please refer to Annotation #1.1, "Adverse Effects, Warfarin," above for additional information about predicting the risk of bleeding for individual patients.

Pregnancy

See Annotation #1.4, "Pregnancy, Warfarin – High Risk" below.

1.3. Precautions, Warfarin

Combined Warfarin and Antiplatelet Therapy

In general, it is not recommended that antiplatelet medications (e.g., aspirin, clopidogrel) be added to warfarin therapy unless there is a strong need for both therapies. Combined use of these agents has been shown to increase bleed risk two- to threefold. Patients with risk factors for atherosclerotic cardiovascular disease (e.g., diabetes, hypertension) and those with chronic stable atherosclerotic cardiovascular disease can usually be started on warfarin with the discontinuation of the antiplatelet therapy.

Circumstances that may necessitate the combined use of antiplatelet drugs and warfarin may include patients with mechanical valves, patients with acute coronary syndrome or patients with recent coronary stents or bypass surgery. This is categorized as a 2C, weak recommendation, by the American College of Chest Physicians (ACCP) *[R]*. However, even in these circumstances, the patient's individual bleeding risk should be taken into account. If bleed risk is prohibitive with combined use, one could consider discontinuing warfarin or decreasing the target INR in order to lower that patient's risks.

Consultation with an anticoagulation expert may be helpful in determining the risks and benefits of combined warfarin and antiplatelet use.

[M], *[R]*

1.4. Pregnancy, Warfarin – High Risk

Recommendations regarding the use of warfarin during pregnancy are difficult due to lack of prospective data. Clinical guidelines are based mainly on retrospective data.

The manufacturer of warfarin states that it is contraindicated during pregnancy secondary to embryopathy associated with use during the first

trimester, weeks 6-12 and CNS abnormalities from exposure during any trimester. The risk of embryopathy appears to be between 4% and 10%. The risk may be lower if the dose of warfarin is less than 5 mg per day.

If the mother is taking warfarin at the time of delivery, the rate of fetal intracranial hemorrhages during delivery is increased. If patients remain on warfarin during pregnancy, warfarin should be discontinued and continuous intravenous unfractionated heparin should be started 2 to 3 weeks prior to delivery *[R]*.

In patients with mechanical heart valves, the decision of whether to continue warfarin or use UFH or LMWH during the first trimester and throughout pregnancy should be made after a discussion with an anticoagulation expert with regards to the risk and benefits *[R]*. For further recommendations, please see the American College of Cardiology/American Heart Association (ACC/AHA) 2008 Guideline Update on Valvular Heart Disease: Focused Update on Infective Endocarditis.

1.5 Breastfeeding, Warfarin

The amount of warfarin in breast milk is too small to affect the baby. As a result, breastfeeding is safe for mothers taking warfarin and for their infants.

1.6 Dosing, Warfarin

Key Points:

- Patients receiving warfarin for the first time should begin at the patient's estimated average daily dose (typically 5 mg/day; range 2.5-7.5 mg/day), with a recheck of the INR in two to three doses.
- Steady-state INR values will not be realized for up to three weeks following a dose adjustment.

[R]

Testing should be obtained before initiation of warfarin:

- Complete blood count (CBC)
- Platelet count
- INR
- Activated partial thromboplastin time (aPTT)
- Creatinine
- Liver enzymes (alanine transaminase [ALT], aspartate transaminase [AST], gamma-glutamyl transferase [GGT])
- Albumin

General Principles of Warfarin Dosing

Except in certain circumstances as noted, loading doses of warfarin should not be used. Warfarin (irrespective of INR) is not fully effective in the first several days of therapy because of a delayed decrease in several circulating clotting factors. Loading doses can increase a patient's risk of supratherapeutic INR and make it more difficult to determine a steady-state dose *[A]*, *[B]*.

For patients sufficiently healthy being treated as outpatients, the ACCP 2012 guidelines suggest initiating warfarin at 10 mg once daily for the first two days followed by dosing based on INRs rather than starting with the estimated maintenance dose. This is categorized as a 2C, weak recommendation, by the ACCP *[R]*.

The FDA approved updated labeling for warfarin. The agency reports that people with variations in two genes, CYP2C9 and VKORC1, are individually responsible for 35% to 50% of the variable dose response to warfarin *[R]*. These genetic variations affect the dose of warfarin that individual patients will need to achieve and maintain therapeutic INRs. This issue is discussed further under "Initiation of Warfarin" in this annotation.

Patients at high risk of thrombosis, such as those with an active thrombotic process (e.g., venous thromboembolism [VTE]) or an underlying malignancy, should be initially treated with concomitant immediate-acting anticoagulant (UFH, LMWH, fondaparinux, DTIs) and warfarin therapy. Patients at lower thrombotic risk (e.g., atrial fibrillation without recurrent thromboembolism) can be initiated on warfarin alone.

Most of the indications for warfarin therapy require a recommended target INR of 2.5, with a therapeutic INR range of 2.0 to 3.0. Examples of clinical indications with this target INR and recommended range include venous thrombosis and pulmonary embolism, chronic atrial fibrillation, mitral bioprosthetic valves and some cases of rheumatic valvular heart disease. Other clinical situations are at higher risk for thromboembolic events and require a target INR of 3.0 with a therapeutic INR range of 2.5 to 3.5. Examples of these clinical indications include mitral mechanical valves and rheumatic mitral valve disease associated with left atrial thrombus.

Please refer to the antithrombotic therapy for atrial fibrillation and valvular disease sections of the ACCP Antithrombotic Therapy and Prevention of Thrombosis, 9th edition for target INR recommendations in specific cardiac situations.

The risk of bleeding for patients on warfarin increases substantially at INR values greater than 4.0. This risk is magnified if one or more risk factors are present. Consider hemorrhagic risk in all dosing decisions. Please refer to Appendix B, "Risk Factors for Bleeding During Warfarin Therapy," in the original guideline document.

There is a significant increase in thromboembolism as INR values decrease below INR 1.7. Clinical risk and past medical history should be considered in all dosing decisions. Higher risk may require more aggressive dosing.

In most cases, holding warfarin for 4 days prior to surgery results in an INR value of 1.2 or less. Expect advanced age and drug interactions to result in a slower decline. Patients with high risk of thromboembolism may need coverage with heparin for a portion of this time.

Some equivalency studies have shown that substitution of generic warfarin for brand name Coumadin® may provide equivalent anticoagulation response if the manufacturer of the generic warfarin has followed the standards set for the name brand *[A]*. Care must be taken to remain with either the brand name product or the same generic product. Do not switch from brand to generic or between generics. If a switch must be made, monitor the INR more frequently.

Prescription and over-the-counter medications can adversely affect the INR response to warfarin. Dietary supplements including herbal or natural remedies can change the INR response to warfarin and/or increase a patient's risk of bleeding. In these instances, additional monitoring may be needed.

Mechanisms of drug-drug interactions occur commonly by the cytochrome P450 enzyme metabolizing system. Metabolism of the object or substrate medication may either be induced or inhibited by the interacting drug. Induction will result in a diminished pharmacodynamic response, while inhibition will result in an increased pharmacodynamic response.

Foods that contain moderate amounts of vitamin K may decrease the INR response to warfarin. Patients should be encouraged to not change their diet while taking warfarin and not change the amount of foods containing vitamin K they normally eat each day. Please refer to Annotation #1.9, "Patient Education, Warfarin," for a guide to educating patients regarding warfarin therapy.

Direct thrombin inhibitors and heparins can affect the INR. See Annotations #4.0-4.9, "Direct Thrombin Inhibitors" for more information.

Initiation of Warfarin

The benefits and risks of the addition of aspirin, heparin and/or a LMWH to warfarin during initiation vary from disease to disease. Please see the NGC summaries of the disease specific ICSI guidelines:

- Diagnosis and Initial Treatment of Ischemic Stroke
- Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS)
- Venous Thromboembolism Diagnosis and Treatment
- Venous Thromboembolism Prophylaxis

Average Daily Dosing Technique (for patients not on heparin)

Average daily dosing technique is useful for patients off UFH and LMWH.

A baseline INR value should be drawn to rule out underlying coagulopathy.

Patients previously taking warfarin can be initiated at the previous dose.

Patients receiving warfarin for the first time should begin at an average dose of 5 mg daily with a recheck of INR in two to three doses. Lower initiation doses should be considered for patients with any of the following factors: age greater than 75 years, multiple comorbid conditions, poor nutrition (low albumin), elevated INR when off warfarin, elevated liver function tests, or changing thyroid status. For patients who weigh more than 80 kg, a higher estimated average initial dose of 7.5 mg may be given. Higher initial dosing nomograms have not shown consistent benefit. Loading doses can increase a patient's risk of supratherapeutic INR and make it more difficult to determine a steady-state dose *[A]*, *[B]*.

If the INR is 2.0 or greater after the first three doses, consider decreasing the dose by one-half. Always search for causes of rapid rise in INR such as drug interactions, poor nutritional status, infection, or systemic disease process.

Subsequent INR values are determined at two to three times weekly for 1 to 2 weeks, then less often depending on the stability of the INR result.

Steady-state anticoagulation occurs between 6 and 12 days. Expect obese patients and patients of advanced age to take longer to reach steady state *[D]*, *[R]*.

Flexible Daily Dosing Technique (for inpatients and outpatients on heparin)

The flexible daily dosing technique is useful for patients on concomitant UFH or a LMWH.

A baseline INR value may be drawn to rule out underlying coagulopathy.

Patients are given daily doses of warfarin, adjusted according to the daily INR, until a weekly dose can be determined *[D]*.

The dose-response relationship is best interpreted when there are at least 16 hours between dose and laboratory draw.

Use of Genomic and Clinical Prediction Rules

The FDA approved updated labeling for warfarin. The agency reports that people with variations in two genes, CYP2C9 and VKORC1, are individually responsible for 35% to 50% of the variable dose response to warfarin *[R]*. These genetic variations affect the dose of warfarin that individual patients will need to achieve and maintain therapeutic INRs.

The CHEST guidelines recommend against routine use of pharmacogenetic testing for patients initiating warfarin. This is categorized as a 1B, strong recommendation, by the ACCP *[R]*. The work group feels that more clinical trials are necessary before recommending routine testing of patients for these genetic variations. There are many other variables that influence a patient's response to warfarin therapy. Most important is that all patients initiating warfarin need frequent, careful monitoring to assess their response to this therapy.

Maintenance Dosing of Warfarin

An assessment of clinical variables known to affect the INR (including a change of patient adherence, change of other medications [e.g., amiodarone], change of food or alcohol consumption, change of activity level) should be made with each dose adjustment. Always search for the cause of out-of-range values and address them before adjusting the dose.

Expect a 15% dose adjustment to result in an approximately 1.0 INR change. Likewise, a 10% dose adjustment will result in an approximate 0.7 to 0.8 INR change.

Steady-state INR values will not be realized for up to three weeks following a dose adjustment.

The ACCP guideline recommends that patients with a single out-of-range INR value less than 0.5 above or below therapeutic range be maintained on the current dose and repeat the INR within 1 to 2 weeks. Use of LMWHs or heparin in this situation is not recommended *[R]*. This is categorized as a 2C, weak recommendation, by the ACCP *[R]*.

If two consecutive weekly INR values are within range and there has not been a change in clinical variables known to affect the INR, the interval between draws may be gradually increased to monthly, and not more than 6 weeks. For patients with consistently stable INRs, the ACCP guideline recommends an INR frequency up to 12 weeks rather than every four weeks. This is categorized as a 2C, weak recommendation, by the ACCP *[R]*.

Options for Dosing Management

Anticoagulation clinics have been shown to significantly reduce patients' risks of adverse events.

Though traditionally warfarin has been monitored at a central laboratory and managed by the patient's physician, new monitoring and management options have emerged.

Anticoagulation clinics staffed by pharmacists and registered nurses have been shown to significantly reduce patients' risks of adverse events.

Computer-assisted dosing has been slow to develop, but may someday improve the quality of anticoagulation adjustments and offer superior management for difficult or high-risk patients *[A]*, *[R]*.

Patient Self-Testing and Self-Management

- Patient self-*testing* is when a patient performs an INR at home and receives dosing instructions from a medical provider (e.g., physician or anticoagulation clinic).

- Patient self-*management* is when a patient performs an INR at home and uses an algorithm to guide dosing, without necessarily interacting with a medical provider *[R]*. Patient self-management is not presently approved by Medicare.

Although patient self-testing of the INR in warfarin therapy has been practiced successfully in Europe for many years, this approach to care has not been widely adopted in the United States. In 2008, the Centers for Medicare and Medicaid Services (CMS) expanded the covered indications for patient self-testing of the INR to include the common conditions of atrial fibrillation and VTE *[NA]*. Despite this change, only 1% of warfarin patients in the United States participate in a self-testing program *[X]*.

A consensus guideline has been published detailing a recommended approach to developing a patient self-testing and/or self-management program *[R]*. Critical elements of a self-testing program include appropriate patient (or caregiver) selection for adequate cognition, vision and dexterity; a structured, face-to-face patient education program carried out by a trained staff; formal patient testing to confirm understanding of required information; weekly patient testing and ongoing supervision by a physician or training center. Coagulometers selected for self-testing should give similar results to the laboratory INR testing. These meters should be compared to the laboratory INR or a central point-of-care laboratory instrument at least annually.

If self-management programs are approved by Medicare in the future, they would require ongoing support from a physician or anticoagulation clinic for a variety of issues including situations where maintaining appropriate anticoagulation were difficult, planned surgical intervention requiring bridging and ongoing education *[R]*.

Warfarin Periprocedural Management

Anticoagulation Bridging

Interruption of chronic warfarin therapy is occasionally needed when patients undergo procedures. To achieve adequate hemostasis, warfarin is held for four to five doses (depending on patient's INR range) prior to procedure. Warfarin is then restarted within 12 to 24 hours following the procedure but does not achieve an adequate anticoagulation effect for at least five days. Therefore, patients who hold warfarin therapy for procedures have a 7 to 10 day period when they are not receiving antithrombotic protection from warfarin. Depending on the patient's circumstances, a decision is sometimes made to "bridge" this interval off warfarin with a shorter-acting parenteral anticoagulant such as intravenous (IV) UFH or LMWH. However, bridge therapy can increase the patient's risk of procedure-related bleeding, especially when given immediately after the procedure. The decision to use short-acting parenteral anticoagulants or simply hold warfarin without bridging takes into account the individual patient's risk of a thrombotic event off warfarin weighed against his/her risk of bleeding complications from the procedure and parenteral anticoagulants. Table 2 in the original guideline document gives examples of cardiac conditions with variable risks of thromboembolic events.

Low Bleeding Risk Procedures

For most dental procedures, a review of the literature has shown that in most cases no change in warfarin is needed *[R]*. It may be reasonable to allow the patient to "drift" to the low end of his/her therapeutic INR prior to a dental procedure with a higher risk of bleeding. Warfarin can be held 2 to 3 days prior to dental procedure to achieve this goal.

Local bleeding may be controlled with a variety of techniques including pressure, biting on tea bags, gelatin sponges and topical thrombin. Other means of local hemostasis control include tranexamic acid mouthwash or epsilon aminocaproic acid packing *[R]*, *[D]*.

Other examples of procedures with low bleeding risk include skin biopsies, ureteral stent placement, paracentesis, and cataract surgery. Patients who have procedures that are of low bleeding risk can be continued on warfarin anticoagulation without interruption.

For gynecologic and orthopedic surgical patients at low risk for bleeding, the warfarin dose may be lowered 4 to 5 days before surgery and the surgery performed at a lower INR (INR 1.3-1.5). The warfarin dose can be increased to the previous dose postoperatively *[R]*. Table 3 in the original guideline document lists low-risk bleed procedures *[R]*.

Procedures considered to have a high bleeding risk include cardiac surgery, neurosurgery, abdominal surgery, spinal anesthesia and surgeries involving major organs. Additional determinants of bleeding risk include advanced age, comorbidities and concomitant use of antiplatelet therapy.

Thrombotic Risk Stratification

The ACCP has generated a grid, shown in Table 4 of the original guideline document, to help define the relative risk of thromboembolism in patients with different criteria for anticoagulation. This may be used as a guide for decision-making when determining when patients might warrant bridging with parenteral anticoagulation versus holding warfarin therapy.

Options for Anticoagulation Management around the Time of Procedures

A summary of options for patients on anticoagulation to consider at the time of procedure is listed in the table below. Clinicians should use their judgment and patient preferences in determining a final course of action.

Table. Perioperative Anticoagulation Management

Patient Bleeding Risk for Procedure		
Patient Thromboembolic Risk	Low	High
Low	Continue warfarin	Hold warfarin 5 days (4 doses) prior to procedure Restart day of procedure
Moderate	Continue warfarin	Hold warfarin 5 days (4 doses) prior to procedure Consider parenteral anticoagulant bridge (LMWH or UFH) • If cardioembolic risk, use therapeutic dosing • If VTE risk, use prophylactic dosing
High	Continue warfarin	Parenteral anticoagulant bridging (LMWH or UFH), therapeutic dosing

LMWH, low-molecular weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

Timing of Anticoagulation Management for Procedures

An example of a bridge protocol for patients receiving therapeutic parenteral anticoagulation therapy is shown in Table 6 of the original guideline document. Please be aware that studies have shown a significant risk for bleeding associated with therapeutic parenteral anticoagulation bridging. Patients should be made aware of both the thrombotic and bleeding risks associated with this approach and be involved in the final decision on bridging. There are no FDA-approved schedules for bridging.

Neuraxial Blockade Management (Spinal/Epidural)

Please see the NGC summary of the ICSI guideline Venous Thromboembolism Prophylaxis.

1.7. Monitoring, Warfarin

Test

The INR is the preferred test for monitoring warfarin therapy. The INR is calculated from the prothrombin time (PT) as follows:

$$(\text{Patient PT}/\text{Mean Normal PT})^{ISI}$$

The mean normal PT is the geometric mean of prothrombin times determined from at least 20 fresh samples obtained from healthy men and women. The International Sensitivity Index (ISI) is a measure of sensitivity of the thromboplastin. The manufacturer will frequently provide an ISI specific for the analyzer used. The ISI can be verified by the local laboratory using certified, reference plasmas *[R]*.

Limitations of INR

There are several recognized limitations of the test, including instrumentation effect on the ISI and erroneous reporting of the ISI by the thromboplastin manufacturer *[R]*.

Timing and Frequency of INR Testing

During initiation and maintenance therapy with warfarin, the INR is best measured at least 16 hours after the dose of warfarin.

In most stable patients, INR determinations can be obtained once or twice monthly. Per ACCP guidelines no more than 12 weeks should elapse between determinations. This is categorized as a 2B, weak recommendation, by the ACCP *[R]*.

Influence of Heparin and Lupus Anticoagulants on the INR

Prothrombin reagents contain a heparin neutralizer; however, presence of high concentrations of heparin in plasma samples (e.g., sample collected shortly after IV heparin bolus, or sample collected above an IV infusion of unfractionated heparin, or sample collected through a

heparin-coated catheter [central venous line or arterial line]) will spuriously prolong the INR.

Prothrombin reagents contain a high concentration of phospholipids; thus, presence of lupus anticoagulants typically does not affect the INR result.

However, there are individual patients in whom lupus anticoagulants may spuriously prolong INR results obtained by some instrument-reagent combinations. In these patients, lupus anticoagulants can cause a prolongation of the PT and INR, resulting in a perceived overestimation of a patient's anticoagulation.

Alternatives to INR in Patients with Lupus Anticoagulants

For patients with a prolonged baseline INR due to a lupus anticoagulant, alternatives to the INR have been evaluated. Measurement of chromogenic factor X levels or factor II levels may be helpful in the monitoring of warfarin therapy in selected patients with lupus anticoagulant *[D]*, *[R]*. Both the chromogenic factor X and factor II levels may not be readily available.

Transitioning from Argatroban to Warfarin

Argatroban significantly prolongs the INR, requiring additional coagulation testing during transition to warfarin. Please refer to Annotation #4.7b, "Monitoring, Parenteral DTI," for further discussion.

Blood Samples

Patient samples should be collected in 109 mmol/L (3.2%) sodium citrate when INR testing is performed on anticoagulated plasma *[B]*, *[R]*.

- The volume of sodium citrate in blood tubes used for collection of plasma INR testing should be adjusted when the patient's hematocrit is greater than 55%. Specimens with a high hematocrit will cause spuriously high INR values unless the citrate volume is adjusted *[R]*.
- Anticoagulated whole blood may be stored spun or unspun at room temperature for up to 24 hours prior to testing *[R]*.

Refer to the original guideline document for information on instruments, including point of care instruments and reagents.

1.8. Correction of Supratherapeutic Anticoagulation/Reversal, Warfarin

Supratherapeutic anticoagulation may occur with patients taking warfarin. Vitamin K may be used to reverse the effects of warfarin; however, vitamin K can lead to warfarin resistance and, subsequently, to an increased risk of thromboembolism.

One must weigh the benefits of reversing anticoagulation with warfarin and associated decreased risk for bleeding against the risk of vitamin K-induced warfarin resistance and associated increased risk for thromboembolism. The ACCP guidelines recommend against the routine use of vitamin K in patients taking warfarin with INRs between 4.5 and 10 with no evidence of bleeding. This is categorized as a 2B, weak recommendation, by the ACCP *[R]*. For patients taking warfarin with INRs greater than 10.0 and with no evidence of bleeding, the CHEST guidelines recommend oral vitamin K. This is categorized as a 2C, weak recommendation, by the ACCP *[R]*.

Important Considerations for Vitamin K Dosing

In an outpatient clinic setting, oral vitamin K is the preferred route of administration.

In a hospital setting, when patients are ill or taking nothing by mouth, intravenous vitamin K may be the preferred route of administration. To avoid anaphylactic reactions, vitamin K should be given over 30 minutes in a mixture of dextrose 5% in water (D5W) 50 mL under monitored conditions. It is not necessary to premedicate with corticosteroids or antihistamines.

Administration of vitamin K by subcutaneous or intramuscular injections is not recommended due to unpredictable absorption which can lead to erratic correction of INR and resistance to warfarin *[B]*, *[C]*, *[R]*.

Refer to Table 7 in the original guideline document for details on correction of supratherapeutic anticoagulation caused by warfarin.

1.9. Patient Education, Warfarin

Mechanism of action of warfarin: it depletes certain coagulation factor proteins in the blood.

Time of day to take warfarin: it should be taken at approximately the same time each day. Due to the short half-life of factor VII and its influence on the INR, this is especially important if the patient will have an INR drawn the next morning.

Explanation of INR, target range, and regular testing.

Signs and symptoms of bleeding and that the provider should be contacted immediately if bleeding signs are present.

Need to notify provider if illness, injury, or change in physical status occurs.

Need to inform all health care providers of anticoagulation therapy, especially if potentially undergoing an invasive procedure, surgery or dental work.

Drug Interactions

- What to do if a new medication is initiated or a medication is discontinued, especially if the interaction with warfarin is unknown: check INR within 3 to 4 days.
- Drugs that affect the absorption of warfarin
- Drugs that increase or decrease the effect of warfarin
- Common over-the-counter medication interactions, including aspirin, NSAIDs, acetaminophen, natural or herbal remedies, laxatives, antacids, and multivitamin preparations containing vitamin K

Role of vitamin K and the importance of consistency of vitamin K-rich foods in the diet rather than avoidance of vitamin K-rich foods.

Importance of minimizing trauma risk associated with activities at high risk for injury

Effect of exercise: increased activity results in decreased effect of the drug.

Effect of personal habits: alcohol, chewing tobacco, etc.

Effect of certain conditions: congestive heart failure, thyroid disease, gastroenteritis, and diarrhea

Importance of self-monitoring: maintain a log of INRs, dose of warfarin, etc.

MedicAlert® bracelet/necklace and warfarin ID card

2. Unfractionated Heparin and Low-Molecular-Weight Heparin
2.0. Introduction, UFH and LMWH

In October of 2009 the FDA notified health care professionals of a change to heparin that standardized the United States Pharmacopeia (USP) unit dose with the World Health Organization (WHO) International Standard unit dose. This change resulted in an approximately 10% reduction in anticoagulant activity compared to heparin prepared using the previous USP Monograph potency. The FDA recommends that health care professionals "exercise clinical judgment in determining the dose of heparin for a patient and consider the clinical circumstances where the potency decrease may require dosage adjustments and more frequent monitoring," particularly when heparin is administered as a bolus intravenous dose and an immediate anticoagulant effect is clinically important. Due to the high inter-patient variability in heparin clearance (+/- 1.18 mL/min/kg) *[R]*, therapeutic heparin dose is highly individualized per patient and highly reliant on PTT or heparin assay monitoring and dose adjustment. Although a small downward bias may be observed overall, built-in prothrombin time/activated clotting time (PTT/ACT) protocols and bolus dose ranges may negate the need for broad, empiric policy change.

Heparin's (UFH, LMWH) anticoagulant effect is due to the presence of a pentasaccharide sequence which potentiates the action of antithrombin leading to inactivation of several clotting factors--primarily factors Xa and IIa. Heparins have relatively rapid onset of action compared to warfarin and are often the first drug used in acute thrombotic situations.

UFH has variable absorption, metabolism, pharmacokinetics, and effects on anticoagulation. Monitoring is required in most patients treated with this drug.

LMWHs are depolymerized byproducts of UFH. Pharmacological advantages of LMWH relate to superior absorption and consistent dose effect response.

2.1. Adverse Effects Including Heparin-Induced Thrombocytopenia of UFH and LMWH

Key Points:

- HIT should be suspected in patients who develop a skin lesion reaction at the injection site, have a systemic reaction to a bolus administration of heparin, or develop a greater than 50% decrease in platelet count from baseline labs while on heparin *[R]*.
- HIT should be suspected if the patient experiences a new thrombotic event within 5 to 14 days of initiating heparin therapy, even if

the heparin has been discontinued *[R]*.

- In non-cardiac post-surgical patients, HIT should be suspected when the platelet count falls 50% from the post-operative platelet count peak *[R]*.
- Following cardiac surgery patients the following two patterns are concerning for HIT:
    1. Drop in platelet count beginning greater than 4 days postoperatively (day of surgery = day 0)
    2. Thrombocytopenia that persists for greater than 4 days after surgery *[R]*

- All heparin should be stopped in patients suspected of having HIT until antibody test results are available.
- If the patient is on concomitant warfarin and HIT is suspected, the warfarin should be stopped, the warfarin effects corrected with vitamin K, and the patient started on direct thrombin inhibitor therapy.

Bleeding

Risk of bleeding increases with treatment-related factors such as dose, duration, and use of thrombolytics and/or antiplatelet agents, and patient-related factors including age over 70 years, recent trauma or surgery, coagulopathy, peptic ulcer, neoplasm, or renal failure.

The rate of major bleeding associated with 5 to 10 days of IV unfractionated heparin in patients with acute venous thromboembolism (VTE) is 0% to 7.0% and the rate of fatal bleeding 0% to 2.0%. The rate of major bleeding associated with 5 to 10 days of subcutaneous LMWH in patients with acute VTE is 0.0% to 0.8%. There is no increased risk of bleeding associated with short-term IV UFH and subcutaneous LMWHs in patients with unstable angina *[A]*, *[R]*.

Heparin-Induced Thrombocytopenia

HIT is an immune-mediated reaction to heparins. It occurs in 2% to 3% of patients treated with UFH and less than 1% of patients treated with LMWH. This syndrome can be associated with paradoxical increased risk for venous and arterial thrombosis. Patients who develop HIT without associated thrombosis will have a significant risk for thrombosis in the subsequent 100 days. Patients with a history of HIT should not be treated with UFH or LMWH *[R]*.

HIT should be suspected in patients who develop a skin lesion reaction at the injection site, have a systemic reaction to a bolus administration of heparin, or develop a greater than 50% decrease in platelet count from baseline labs while on heparin. HIT should also be suspected if the patient experiences a new thrombotic event within 5 to 14 days of initiating heparin therapy, even if the heparin has been discontinued *[R]*.

Delayed-onset HIT is an increasingly recognized form of this disorder. Patients with delayed-onset HIT typically present with thromboembolic complications one to two weeks (studies show the range 5 to 40 days) after receiving their last dose of LMWH or UFH. They frequently display mild or moderate thrombocytopenia. When HIT is not recognized as the etiology of the thromboembolic complication, the patient is frequently rechallenged with heparin, causing significant worsening of the thrombosis, as well as the thrombocytopenia. These patients typically have very high titers of HIT-related antibodies. The possibility of delayed onset HIT should be considered in any patient presenting with thromboembolism after a recent hospitalization.

Patients suspected of having any form of HIT should have their heparin stopped while antibody testing for HIT is performed. Patients with a high clinical probability of having HIT should be treated with an appropriate alternative anticoagulant before antibody test results are available. DTIs are the alternative anticoagulant of choice for patients with HIT. Three generics are FDA approved: argatroban, lepirudin (lepirudin will no longer be manufactured after May 2013), and most recently, bivalirudin *[R]*.

The off-label use of fondaparinux has been suggested as an alternative to DTI therapy in HIT given its long half-life and lack of significant effect on the INR as well as the protein C pathway *[R]*. Although fondaparinux therapy can result in development of anti-PF4/heparin antibodies, they usually do not result in platelet activation. Three cases of HIT related to fondaparinux therapy have been reported *[D]*. Further study is required prior to recommendation of fondaparinux as a therapy in HIT.

There is no data to support use of the new oral anticoagulants like dabigatran or rivaroxaban in HIT *[R]*.

Warfarin therapy alone is contraindicated in the setting of acute HIT *[R]*. If a patient is receiving warfarin when there is a high clinical probability of HIT, the warfarin should be stopped. The warfarin effect should be reversed with vitamin K, and DTI therapy should be initiated. Studies have demonstrated that the manufacturer-recommended dosages for argatroban are too high. Therefore, lower doses are recommended (see Annotation #4.6b, "Dosing, Parenteral DTI"). Low maintenance doses of warfarin can be restarted during DTI therapy after the platelet count has significantly improved and there is clinical improvement in the patient's thrombosis. There should be at least a 5-day overlap of the DTIs and warfarin. The DTI therapy should be continued until the platelet count stabilizes *[R]*.

Please refer to Annotations #4.0-4.9b, "Direct Thrombin Inhibitors (DTI)," for more information.

2.2. Contraindications, UFH and LMWH

- Active major bleeding including intracerebral hemorrhage within past 2 weeks, subarachnoid hemorrhage until definitively treated
- Thrombolytics given within past 24 hours for acute stroke
- Hypersensitivity to heparin or pork products
- HIT. Patients with a history of HIT who require cardiac surgery may receive UFH for the procedure if they are antibody-negative for platelet factor 4 (PF4). Alternate anticoagulants should be used for preoperative and postoperative anticoagulation *[R]*.

2.3. Precautions, UFH and LMWH

Active or recent history of gastrointestinal ulceration and hemorrhage

Bacterial endocarditis

Bleeding diathesis

Concomitant therapy with agents that inhibit platelets

Congenital or acquired bleeding disorders

Hemorrhagic stroke

Status post brain, spinal, or ophthalmologic surgery

Uncontrolled arterial hypertension

Diabetic retinopathy

Impaired renal function (creatinine clearance [CrCl] <50 mL)

Obese patients: Dose capping is not recommended and twice daily dosing may be preferable for Lovenox.

Refer to the table in section 2.3 of the original guideline document to distinguish dosing differences between CrCl <30 mL/min and CrCl 30-50 mL/min for enoxaparin and dalteparin.

2.4. Pregnancy, UFH and LMWH

Adverse Effects in Pregnancy

UFH and LMWH do not cross the placenta and therefore do not cause teratogenicity or fetal bleeding, though bleeding at the uteroplacental junction is possible *[R]*.

Patients with mechanical heart valves who are pregnant are at high risk and should be managed by an anticoagulation expert. A study has shown that two pregnant patients with mechanical heart valves had thrombotic complications when treated with LMWH. Because of this, the FDA and the manufacturer have warned that enoxaparin is not presently indicated for use in prophylaxis for heart valve patients who are pregnant. However, the available data sets, clinical trials, reviews, and registry data suggest that, compared with UFH, LMWHs may be safe and effective agents in pregnant women with mechanical heart valves *[M]*.

The ACCP recommends that women requiring long-term anticoagulation with warfarin who are attempting pregnancy be monitored with frequent pregnancy tests. They recommend substituting UFH or a LMWH for warfarin when pregnancy is achieved *[R]*. LMWHs cause less HIT and bone loss during pregnancy than UFH.

The pharmacokinetics of LMWH in pregnancy are significantly altered. Consideration should be given to monitoring the anti-Xa activity at 12 to 15 weeks and 30 to 33 weeks.

When possible, patients using UFH or a LMWH should have a planned delivery. UFH should be discontinued 6 hours prior to a planned delivery. LMWH should be discontinued 24 hours prior to a planned delivery.

2.5. Breastfeeding, UFH and LMWH

Heparin is not secreted in breast milk and can be given safely to nursing mothers *[R]*.

2.6. Dosing

2.61. UFH Dosing

Anaphylaxis occurs in 1% of patients who have previously received protamine (such as neutral protamine Hagedorn [NPH] insulin). Other adverse effects include hypotension. *[R]*

Testing should be obtained before initiation of UFH:

- CBC/platelet count
- INR
- aPTT
- Creatinine

Obtain if there is clinical suspicion of abnormal results based on patient history and physical:

- Liver enzymes (alanine transaminase [ALT], aspartate amino transferase [AST], gamma glutamyl transferase [GGT])
- Albumin

Dosing — Prophylactic

See the NGC summary of the ICSI guideline Venous Thromboembolism Prophylaxis

Dosing — Therapeutic

Weight-based, institution-specific nomograms are strongly recommended for patients on therapeutic intravenous UFH. Several heparin therapy management protocols have been shown to achieve therapeutic anticoagulation (as measured by aPTT levels) more rapidly than historical controls. Several acceptable protocols are discussed in the literature. These include a fixed initial maintenance dose, two levels of the initial maintenance dose based on patient's risk of bleeding, and several levels of the initial maintenance dose based on patient's body weight *[A]*, *[B]*. Each institution must develop its own nomograms based upon their unique specific therapeutic ranges.

A standard weight-based protocol for heparin administration should not be used for patients receiving parenteral platelet receptor glycoprotein IIb/IIIa antagonist (abciximab, tirofiban, eptifibatide) and/or thrombolytics (alteplase, reteplase, tenecteplase, streptokinase). Treating physicians should refer to the specific agent's package insert or their institution protocols for the specific agent's heparin protocol. Before administering UFH, the patient's height in centimeters and weight in kilograms, and any adverse reactions to drugs or food, including a description of the reaction, should be noted.

Initiation of UFH

An initial bolus dose of heparin is recommended followed by IV infusion, with the exception of acute stroke. The use of heparin in patients with acute stroke is evolving. See the NGC summary of the ICSI guideline Diagnosis and Initial Treatment of Ischemic Stroke. Note the time of initial heparin bolus.

After initial IV bolus of heparin, begin maintenance drip per institutional protocols.

For patients with acute venous thromboembolism, ACCP guidelines recommend starting warfarin therapy on day one or day two of UFH or LMWH heparin therapy rather than waiting several days to start. This is categorized as a 2C, weak recommendation, by the ACCP *[R]*.

Maintenance

Obtain an aPTT level or heparin assay 6 hours after the initiation of IV heparin drip. Adjust the IV drip according to institutional protocols.

2.62. LMWH Dosing

Key Point:

- Prophylactic doses are lower than therapeutic and carry lower bleeding risks. However, in patients with acute thrombosis and cardioembolic risks, therapeutic dosing is generally recommended.

Testing should be obtained before initiation of LMWH:

- CBC/platelet count
- INR
- aPTT
- Creatinine

Obtain if there is clinical suspicion of abnormal results based on patient history and physical:

- Liver enzymes (ALT, AST, GGT)
- Albumin

LMWH should not be administered by intramuscular injection.

Therapeutic doses of a LMWH are different from prophylactic doses.

Doses of different LMWHs are not interchangeable *[R]*.

The anticoagulant effect of LMWH can extend beyond 24 hours after administration.

The dose should be modified for patients with impaired renal function. It may be necessary to monitor the anti-Xa level in these patients. LMWHs are relatively contraindicated in patients with a creatinine clearance less than 30 mL/min or who are receiving dialysis.

The optimal dose of LMWH has not been established in patients with low body weight (less than 50 kg) (possibly higher than usual dose), obesity (possibly lower than usual dose) or pregnancy (changing dose due to changing creatinine clearance). It may be necessary to monitor the anti-Xa level in these patients *[D]*.

Prophylactic doses of the LMWHs are less than therapeutic doses and carry lower bleeding risks. However, in patients with acute thrombosis or increased thrombosis risk, therapeutic dosing is generally necessary.

Please see the NGC summaries of the ICSI guidelines for the disease specific recommendations:

- Diagnosis and Initial Treatment of Ischemic Stroke
- Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS)
- Venous Thromboembolism Diagnosis and Treatment
- Venous Thromboembolism Prophylaxis

2.7. Monitoring

2.71. UFH Monitoring

UFH treatment of thrombosis can be monitored using an aPTT or heparin assay. The recommended test for monitoring UFH, including the therapeutic range for the test, should be provided by the laboratory. Of note, aPTT results vary among institutions due to differences in laboratory instruments and reagents. The aPTT therapeutic range should correspond to a plasma heparin concentration of 0.3 to 0.7 units/mL by an anti-Xa inhibition assay (0.2 to 0.4 units/mL by protamine titration assay) *[R]*.

Heparin assays are being increasingly used for monitoring UFHs in the treatment of venous thromboembolism. The suggested target therapeutic range is 0.35 to 0.7 units/mL by the anti-Xa inhibition assay. Monitoring UFH using a heparin assay may be indicated when the expected aPTT prolongation is not observed despite high doses of UFH (greater than 35,000 units UFH in 24 hours), when the pretreatment aPTT is prolonged or when a lupus anticoagulant has been previously documented in the patient *[R]*.

Patients receiving UFH or a LMWH should be monitored for HIT. A platelet count of less than 50% of baseline or the postoperative peak during heparin therapy may indicate the development of HIT. The recommended frequency of monitoring is dependent upon the patient's risk of developing HIT. Postoperative patients receiving prophylactic or therapeutic UFH have the highest risk of HIT requiring platelet monitoring every other day from day 4 to 14 or until the heparin is discontinued. Any patient receiving therapeutic UFH, medical and obstetrical patients receiving prophylactic UFH, medical and obstetrical patients receiving LMWH after a dose of UFH, postoperative patients receiving prophylactic LMWH, and postoperative/critical care patients receiving UFH flushes are at lower risk for developing HIT, but still warrant every-other-day platelet count monitoring between day 4 and 14 or until the heparin is discontinued.

Medical and obstetrical patients receiving LMWH, medical patients receiving UFH flushes and patients receiving therapeutic or prophylactic fondaparinux are at very low risk of developing HIT and routine platelet count monitoring is not needed. Patients receiving outpatient heparin therapy should be instructed to seek immediate medical attention if the signs or symptoms of HIT develop.

Patients who have been exposed to heparin within the past 100 days and patients with unclear heparin exposure histories should undergo baseline platelet count testing with repeat platelet count testing within 24 hours of the first heparin dose to evaluate the possibility of rapid onset HIT.

See Annotation #2.1, "Adverse Effects, Including Heparin-Induced Thrombocytopenia of UFH and LMWH," for more information.

[R]

2.72. LMWH Monitoring

Patients receiving LMWH are at lower risk of developing HIT than patients receiving UFH. The need for platelet count monitoring during LMWH therapy depends on the indication for anticoagulation. Postoperative patients receiving LMWH and medical/obstetrical patients receiving LMWH following at least one dose of UFH (including UFH IV flushes) within the past 100 days infrequently experience HIT. Therefore, a baseline platelet count followed by platelet counts every 2 to 3 days is recommended until the LMWH is discontinued or until day 14 of therapy, whichever comes first.

Medical and obstetrical patients receiving only LMWH rarely develop HIT. After a baseline platelet count, routine platelet count monitoring is not required. If there is clinical uncertainty about whether the patient may have received UFH, community standard is to monitor platelet counts monthly.

All patients receiving any form of heparin should be instructed to immediately seek medical attention if signs or symptoms of venous thromboembolism are suspected *[R]*.

2.8. Correction of Supratherapeutic Anticoagulation/Reversal

2.81. UFH, Correction of Supratherapeutic Anticoagulation/Reversal

Protamine sulfate administered by slow IV infusion over 10 minutes reverses the anticoagulation effects of UFH.

Bolus dose of UFH (units) divided by 100 = protamine dose
Hourly infusion rate of UFH (units) divided by 40 = protamine dose

2.82. LMWH, Correction of Supratherapeutic Anticoagulation/Reversal

No agent, including fresh frozen plasma (FFP) and vitamin K, is effective for complete reversal of supratherapeutic anticoagulation with LMWH. Reversal of LMWH with protamine sulfate is incomplete, with neutralization of 60% to 75% at most. However, protamine should be considered for patients with severe life-threatening bleeding. Anaphylaxis occurs in 1% of patients who have previously received protamine (such as NPH insulin). Other adverse effects include hypotension *[R]*.

Administering protamine slowly can minimize adverse reactions to protamine, such as hypotension or bradycardia *[R]*. Note: Excessive protamine doses may worsen bleeding potential *[R]*.

If LMWH has been administered within the last 8 hours (unlabeled use):

Enoxaparin

- First dose: 1 mg protamine for each 1 mg of enoxaparin. Administered by slow IV infusion over 10 minutes *[R]*.
- Second dose: 0.5 mg protamine for each 1 mg of enoxaparin. Administered by slow IV infusion over 10 minutes. Do not exceed 50 mg in 10 minutes *[R]*.

Dalteparin

First dose: 1 mg protamine for each 100 anti-Xa units of dalteparin. Administered by slow IV infusion over 10 minutes. Do not exceed 50 mg in any 10 minutes *[R]*.

Smaller doses are needed if the LMWH was administered more than 8 hours prior.

2.9. Patient Education

2.91. UFH, Patient Education

Importance of understanding heparin assays, INRs and target ranges

Know and watch for signs of bleeding

2.92. LMWH, Patient Education

Over-the-counter and prescription drugs that should not be taken while on LMWH

Importance of understanding heparin assays, INRs, and target ranges

Know and watch for signs of bleeding

Proper technique for injecting LMWH

Restrictions for other conditions including deep vein thrombosis, stroke, or stable coronary artery disease. Please refer to related ICSI guidelines for more information.

Importance of adhering to prescribed regimen

Tables of patient education resources, along with patient and provider-oriented Web sites, are included in the "Implementation Tools and Resources Table" of the original guideline document.

3. Synthetic Pentasaccharide (Fondaparinux)

3.0. Introduction, Synthetic Pentasaccharide

Fondaparinux is a synthetic compound composed of the essential pentasaccharide sequence that selectively inhibits factor Xa.

3.1. Adverse Effects, Synthetic Pentasaccharide

Anemia has been reported in some patients receiving fondaparinux. Asymptomatic elevation in AST and ALT associated with an increase in bilirubin can occur in a small percentage of patients.

3.2. Contraindications, Synthetic Pentasaccharide

Active major bleeding including intracerebral hemorrhage within past 2 weeks, subarachnoid hemorrhage until definitively treated.

Bacterial endocarditis

Severe renal impairment defined by CrCl (Cockroft-Gault) <30 mL/minute

Secondary increased risk for major bleeding episodes

Thrombolytics given within past 24 hours for acute stroke

Fondaparinux has a long elimination half-life and there is no antidote for reversal; therefore, patients who may require rapid reversal are not candidates for this therapy.

3.3. Precautions, Synthetic Pentasaccharide

Fondaparinux should be administered according to recommended regimen, especially with respect to timing of the first dose after surgery.

In hip fracture, hip replacement, knee replacement, or abdominal surgery, clinical studies show that the administration of fondaparinux before 6 hours after surgery has been associated with increased risk of major bleeding.

Precautions

- Active or history of recent gastrointestinal ulceration and hemorrhage
- Bleeding diathesis
- Concomitant therapy with agents that inhibit platelets
- Congenital or acquired bleeding disorders
- Fondaparinux is not recommended for patients with platelets less than 100,000/mm^3.
- Hemorrhagic stroke
- Status recent post brain, spinal, or ophthalmologic surgery
- Uncontrolled arterial hypertension
- Diabetic retinopathy
- Needle guard of the prefilled syringe contains dry natural latex rubber; it is possible but not necesÂsary for the administration that the needle guard may come in contact with the patient and pose an allergy risk
- Renal impairment (CrCl 30-50 mL/min)

3.4. Pregnancy, Synthetic Pentasaccharide

The safety of fondaparinux in pregnant women is unknown. Limited clinical experience suggests that fondaparinux may cross the placental barrier, resulting in low but measurable anti-Xa activity in the umbilical cord *[R]*.

3.5. Breastfeeding, Synthetic Pentasaccharide

Animal studies have shown secretion of fondaparinux in breast milk. It is unknown if humans secrete fondaparinux in breast milk.

3.6. Dosing, Synthetic Pentasaccharide

Testing should be obtained before initiation of fondaparinux:

- CBC/Platelet count
- INR
- aPTT
- Creatinine

Obtain if there is clinical suspicion of abnormal results based on patient history and physical:

- Liver enzymes (ALT, AST, GGT)
- Albumin

Therapeutic doses are different than prophylactic dosing.

The optimal dose of fondaparinux has not been established in patients with obesity (possibly lower than usual dose). It may be necessary to monitor the anti-Xa level in these patients *[D]*.

See Table 8 in the original guideline document for information on FDA approval status, indications, and dosing of fondaparinux.

Please refer to the NGC summaries of the ICSI guidelines Venous Thromboembolism Diagnosis and Treatment and Venous Thromboembolism Prophylaxis for more information.

3.7. Monitoring, Synthetic Pentasaccharide

The heparin assay (anti-Xa) has been used to monitor effects of fondaparinux; however, in most clinical situations, monitoring may not be necessary. Indications for monitoring of fondaparinux include patients weighing over 180 kg or those in whom the level of anticoagulation needs to be checked prior to a procedure.

A platelet count should be obtained prior to the initiation of fondaparinux. Antibodies to fondaparinux rarely interact with platelet factor 4. There are rare reports of HIT associated with fondaparinux *[R]*. Fondaparinux is not recommended for patients with platelets less than 100,000 mm^3 due to the overall increased risk of bleeding.

Fondaparinux may cause transient elevations in serum aminotransferases. This effect is reversible and routine monitoring is not recommended.

Additional information on fondaparinux is included in the NGC summary of the ICSI guideline Venous Thromboembolism Prophylaxis.

3.8. Correction of Supratherapeutic Anticoagulation/Reversal, Synthetic Pentasaccharide

There is no antidote for excessive bleeding due to fondaparinux. Recombinant factor VIIa (rFVIIa) has shown promise as a possible antidote in studies utilizing healthy volunteers. rFVIIa treatment can be complicated by thrombosis. Up to 7% of patients with acute intracerebral hemorrhage who received rFVIIa therapy experienced an adverse thromboembolic event *[A]*, *[R]*. Enzymes capable of degrading heparin have also been investigated as a future treatment for excessive bleeding due to fondaparinux *[A]*, *[R]*, *[NA]*.

3.9. Patient Education, Synthetic Pentasaccharide

Importance of understanding fondaparinux

Know and watch for signs of bleeding.

Proper technique for injecting fondaparinux

Restrictions for other conditions including deep vein thrombosis, stroke, or coronary artery disease. Please refer to the related ICSI guidelines for more information.

Importance to adhering to prescribed regimen

4. Direct Thrombin Inhibitors

4.0. Introduction, DTI

DTIs--argatroban, bivalirudin, lepirudin, dabigatran--are a relatively new class of anticoagulant drugs. (Lepirudin will no longer be manufactured after May 2013.) They exert their anticoagulant effect by directly attaching to and inhibiting both free and fibrin-bound thrombin. Potential advantages of these drugs over UFH are inhibition of fibrin (clot)-bound thrombin, a more predictable anticoagulant response, and no effect on platelet factor 4. Parenteral DTIs have been available for nearly a decade and are used most frequently in cardiovascular procedures and for the treatment of patients with HIT. The oral direct thrombin inhibitor, dabigatran was recently FDA approved for use in patients with non-valvular atrial fibrillation. Consultation with a hematologist or anticoagulation expert may be helpful when using these new anticoagulant drugs because of both drug and disease complexities.

4.0a. Key Considerations for Dabigatran

- FDA approved for use only in non-valvular atrial fibrillation as an alternative to warfarin for stroke prevention *[R]*.
- Patients most likely to benefit from dabigatran are patients unable to achieve and sustain a stable INR or those unable to use warfarin due to management issues *[A]*.
- Like warfarin, it requires the same careful risk/benefit assessment for patients at great risk for hemorrhage *[R]*.
- Caution should be used in patients with CrCl <30 mL/min as drug accumulation will occur and there is no clinical experience in this patient population *[R]*.
- Prior to procedures the drug must be held, the duration of which depends on a patient's renal clearance and bleed risk from procedure *[R]*.

Dabigatran is rapidly absorbed with peak dabigatran levels achieved within 2 to 4 hours. The bioavailability of dabigatran following oral administration of dabigatran etexilate is between 3% and 7%. The half-life of dabigatran is 12 to 17 hours, and steady-state concentrations are reached within 2 to 5 days after multiple doses. Dabigatran is renally eliminated so clearance is significantly influenced by renal function.

Refer to the original guideline document for product care information.

4.1a. Adverse Effects, Dabigatran

Side Effects

Bleeding

Although overall bleed risk was similar to warfarin, there was a significantly higher incidence of gastrointestinal bleeding while a significantly lower incidence of intracranial hemorrhage in the patients taking dabigatran. Also demonstrated in a subgroup analysis was a trend toward a higher incidence of major bleeding in patients 75 years of age and older on dabigatran.

Dyspepsia

A significant (5.5%) number of patients in the trial experienced a severe form of dyspepsia on dabigatran. Elevation of ALT or AST greater than three times the upper limit of normal was similar for both doses of dabigatran and warfarin.

Myocardial Infarction

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial also demonstrated a statistically significant increase in the rate of myocardial infarction in patients treated with dabigatran (0.7% per year) as compared to a rate of 0.5% per year in patients treated with warfarin. This translated into a relative risk of 1.38 (95% confidence interval, 1.00-1.91; P=0.048). Further analysis *[A]* was undertaken by reviewing pooled data from multiple trials, the largest being RE-LY, to look at this effect. The analysis revealed that among patients with atrial fibrillation, warfarin may result in a lower risk of myocardial infarction. The data suggests there may be an intrinsic myocardial protective effect from warfarin as opposed to non-warfarin anticoagulants.

4.2a. Contraindications, Dabigatran

Active Pathological Bleeding

Patients with prohibitive bleed risks were not included in studies of dabigatran. As with all anticoagulants, extreme caution should be used in giving dabigatran to patients with bleeding diatheses, falls risk, alcohol abuse or compliance issues. An individual patient's risk of thrombosis versus risk of bleeding needs to be assessed before use of this or any anticoagulant.

Pregnant patients and those with valvular heart disease have not been studied and are not yet candidates for this drug.

Dose adjustment or avoidance of drug should be considered in patients with severe renal insufficiency, especially if the patient's kidney function is in flux.

4.3a. Precautions, Dabigatran

Drug Interactions

Similar to other anticoagulants, aspirin and other anti-platelet agents have been associated with a significant increase in risk for hemorrhagic complications. Unless strongly indicated anti-platelet agents should be avoided in patients taking dabigatran.

Drugs that inhibit p-glycoprotein (e.g., amiodarone, clarithromycin, diltiazem, verapamil) can increase the area under the drug plasma concentration curve (AUC) of dabigatran. Administering dabigatran more than 2 hours before a p-glycoprotein inhibitor may minimize the effect of the inhibitor on dabigatran absorption. Drugs that induce p-glycoprotein (e.g., rifampin) decrease the AUC of dabigatran. Separating the dose of dabigatran and a p-glycoprotein inducer is not thought to minimize the magnitude of the interaction. Therefore, the concomitant use of dabigatran and p-glycoprotein inducers should be avoided if possible *[X]*.

Administration of dabigatran etexilate capsules with pantoprazole resulted in a reduction of dabigatran's AUC by 20% to 30% and its peak concentration by 45% *[A]*, *[B]*, *[X]*. In the RE-LY trial, concomitant use of proton pump inhibitors and H2 receptor antagonists did not appreciably change the trough concentration of dabigatran *[A]*.

4.4a. Pregnancy, Dabigatran

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women.

4.5a. Breastfeeding, Dabigatran

It is not known whether dabigatran is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when dabigatran is administered to a nursing woman (package insert, as of February 2012).

4.6a. Dosing, Dabigatran

The FDA approved dose of dabigatran for use in non-valvular atrial fibrillation is 150 mg twice daily for patients with CrCl >30 mL/min and 75 mg twice daily in patients with CrCl of 15 to 30 mL/min. The lower renal dose is based on pharmacokinetic data, and there is no clinical experience available. Use in patients with CrCl <15 mL/min or patients receiving dialysis is not recommended. If a dose is missed, and the next dose is due within the next 6 hours, the patient should wait until the next scheduled dose. For example, if the 8:00 a.m. morning dose is missed, and the patient realizes this at 4:00 p.m., then it is recommended that the patient wait until the next dose at 8:00 p.m. However, if the patient realized at 11:00 a.m. that the 8:00 a.m. dose was missed, then the dose can be taken at 11:00 a.m.

Indications

Atrial Fibrillation

A subgroup analysis of the RE-LY study demonstrated that the majority of the benefit of dabigatran was seen when compared to warfarin patients who were poorly controlled. These poorly controlled warfarin patients had the greatest proportion of bleeding and thrombotic complications.

Perioperative Management

Pre-Procedure Management

- The time interval between discontinuing dabigatran and surgical intervention is based on the risk of bleeding and the patient's renal function. This time interval will be longer in individuals with decreased renal function.
- In patients with normal renal function (creatinine clearance >50 mL/min), discontinue dabigatran at least 24 hours prior to the procedure. However, for patients undergoing an intervention considered to have a high risk for bleeding, dabigatran should be discontinued 2 to 4 days prior to the intervention.
- For patients with estimated creatinine clearance between 30 to 50 mL/min, dabigatran should be discontinued at least 48 hours before the procedure; for high bleeding risk situations, dabigatran should be discontinued at least 4 days before the procedure.
- For patients with estimated creatinine clearance less than 30 mL/min, dabigatran should be discontinued for at least 5 days or longer.
- In patients at high risk of bleeding, a thrombin time (TT) can be performed 6 to 12 hours prior to surgery. A normal TT indicates that no drug is present *[R]*. However, the TT does not accurately reflect plasma dabigatran concentrations, so it is not useful in providing an estimate of risk for surgical hemorrhage.

Post-Procedure Management

- It should be noted that, unlike warfarin, the anticoagulant effect of dabigatran occurs within 1 hour (if taken on an empty stomach) or 3 hours (if taken with a meal) after drug ingestion *[NA]*.
- Timing of resumption of dabigatran after the procedure needs to be tailored to the procedure and its postoperative bleed risk.

Bridging for Warfarin Patients

At present, there is no experience with the use of dabigatran as a bridging agent (to replace heparin products) for patients on chronic warfarin therapy undergoing procedures. Because of its effect on the INR, dabigatran could potentially interfere with the use of flexible dosing protocols used to establish warfarin dosing during initiation. Heparin products are considered the preferred anticoagulants to use with warfarin during these circumstances.

Cardioversion

In a subgroup analysis of patients who underwent cardioversion while participating in the RE-LY trial, dabigatran had a low incidence of stroke and major bleeding within 30 days of cardioversion and was comparable to warfarin patients. Dabigatran was considered a safe alternative to warfarin in patients requiring cardioversion *[A]*.

4.7a. Monitoring and Effect on Laboratory Testing, Dabigatran

Routine monitoring of dabigatran is not required. Specialized laboratory assays (ecarin clotting time [ECT], dilute thrombin time [dTT]) are required for accurate assessment of plasma dabigatran levels; however these assays are not widely available. Dabigatran prolongs the clotting times of routine, more widely available assays (TT, activated clotting time [ACT], PT, aPTT). However, these assays do NOT reliably predict plasma dabigatran levels and do not provide an accurate assessment of risk of surgical hemorrhage in patients on dabigatran. The information provided by these assays is limited to whether there is residual dabigatran effect or not.

4.8a. Correction of Supratherapeutic Anticoagulation/Reversal, Dabigatran

NOTE: Consensus-based statements comprise the content of this section on dabigatran. It is important to note that, at the time of writing, there was little data to support these consensus-based recommendations.

Laboratory Testing and Dabigatran

Indications for laboratory testing:

Currently, therapeutic monitoring is not indicated.

Laboratory assays:

Laboratory assays may be broadly categorized into generally available tests and specialized laboratory assays.

- Generally available tests
  These include PT, aPTT, and TT. Dabigatran prolongs these assays; however, the degree of prolongation does NOT reliably predict plasma dabigatran levels nor does it provide an accurate assessment of risk of surgical hemorrhage in patients on dabigatran. The information provided by these assays is limited to whether there is residual dabigatran effect or not. Note: A normal PT or aPTT does not exclude the possibility of residual dabigatran. The thrombin time is typically very sensitive and, again, only provides information on presence or absence of residual drug.

- Specialized laboratory assays
  These include ECT, dTT and ACT. When appropriately calibrated, the ECT and dTT generally provide reliable information on plasma dabigatran levels; however these assays are not widely available. In addition there is currently no information on plasma dabigatran levels and risk of hemorrhage and/or the safety of surgical or other invasive interventions.

Management of Bleeding

- There are limited options for management of bleeding on dabigatran as there is no antidote for reversal of the anticoagulation effect of dabigatran.
- If dabigatran was consumed within 2 hours of presentation, activated charcoal, at standard doses, should be considered *[R]*.
- Hemodialysis is the only known intervention that reduces plasma dabigatran concentration. Approximately 60% of dabigatran is removed after 4 hours of dialysis *[B]*, *[A]*. But, the dabigatran volume of distribution is 50 to 70 L, and a rebound increase in plasma levels of dabigatran may occur after hemodialysis. Thus, close observation and follow-up is needed given that the patient will likely

need more dialysis.
- FFP infusion will not reverse the anticoagulation effect of dabigatran, as the drug will inhibit thrombin in the transfused plasma. (It is important to note that the prolonged clotting times on dabigatran are a reflection of thrombin [factor II] inhibition and not a clotting factor deficiency.)
- As a last resort, one could consider use of procoagulant hemostatic agents such as rFVIIa activated or non-activated prothrombin complex concentrates (PCC). These have been shown to shorten clotting times in vitro and in the rat model; however, they did not reduce blood loss in the rat model *[R]*. In healthy subjects, clotting times remained prolonged after PCC infusion, showing inadequate reversal of anticoagulation *[A]*.

The ICSI work group has included rFVIIa or PCC as options to help with clot formation at the site of bleeding. They do not reverse the drug, the correct dose is unknown and there is no FDA approval for this use. Thrombosis is a known side effect of rFVIIa and PCC.

Protocol for Management of Bleeding on Dabigatran

Consensus-Based Protocol for Bleeding Management

Note:

> - Primary use would be in the emergency room and hospital settings where adult patients on dabigatran are bleeding.
> - Consensus-based statements comprise the content of this section on dabigatran. It is important to note that, at the time of writing, there was little data to support these consensus-based recommendations.

- There is no specific agent to reverse the drug.
- Plasma will not reverse the drug as dabigatran will inhibit thrombin in transfused plasma.
- The only way to remove the drug is dialysis, but this has limited efficacy.
- There is very little data to help guide us in managing bleeding complications on the drug.

Note:

> - All clotting times may be abnormal on dabigatran.
> - TT is the most sensitive to the drug.
> - Fibrinogen activity testing may not be reliable on dabigatran.
> - Clotting times do not accurately reflect drug levels.

For minor bleeding

- Evaluate drug compliance, change in renal function, whether anatomical defects explain hemorrhage.
- Use local measures to control the bleeding.
- Keep hydrated.
- Replace fluids and blood products as needed.
- Clinical judgment to hold or continue dabigatran. Stopping the drug will decrease the bleeding risk. Weigh the risk of stroke and the severity of the bleeding. Consider additional factors, such as duration of the drug effects (1 to 2 days in patients with normal renal function, but can be >5 days with impaired renal function) and the onset of action when restarting (peak activity within two to four hours).

For severe or life-threatening bleeding

- Stop dabigatran.
- Lab testing
  - CBC, platelet count, LFT, aPTT, INR, TT, creatinine and fibrinogen activity.
  - If TT is normal no drug is present.
  - Repeat testing per institutional protocols or, at a minimum, every 4 to 6 hours until bleeding has stopped.
- Control the bleeding site and supportive care of patient.
- Contact surgery or interventional radiology for embolization.
- Administer activated charcoal if the drug has been given within 2 hours.
- Consider dialysis, can remove 60% of the drug
  - Contact renal team.
  - Place dialysis catheter under ultrasound guidance.
- Blood transfusion
  - Transfuse red blood cells (RBCs) per institutional guidelines or to keep hemoglobin (Hgb) >8 gm/dL

    - After the 4th unit of RBCs, start giving RBCs and plasma on a 1:1 ratio (to avoid a dilutional coagulopathy).
    - Cryoprecipitate, give 10 units after the 8th unit of RBCs, 4th unit of plasma – may not need cryoprecipitate if fibrinogen activity is >100 mg/dL.
- rFVIIa or PCC could be considered if bleeding is life-threatening. They do not reverse the drug and the correct dose is unknown. Thrombosis is a potential side effect of both rFVIIa and PCC.

4.9a. Patient Education, Dabigatran

- Instruct patient to promptly report signs/symptoms of prolonged or excessive bleeding.
- Advise patient to notify physician or dentist of medication use prior to surgical procedures.
- Drug may cause unusual bruising, dyspepsia and gastritis-like symptoms.
- Tell patient not to discontinue the drug unless directed by a physician.
- Instruct patient to store drug in original bottle or blister package, not in any other container (e.g., pill boxes or organizers). Patient should open only one bottle at a time, remove only one capsule at the time of use, immediately close the bottle tightly after use, and date the bottle to expire 90 days after opening.
- Counsel patient to consult health care professional prior to new drug use (including over-the-counter and herbal drugs) as bleeding risk may increase with certain drugs (e.g., aspirin, NSAIDs).
- Instruct patient to take a missed dose as soon as possible, but if next dose is due in less than 6 hours, skip the missed dose. Patient should not take two doses at the same time.

4.0b. Key Considerations, Parenteral DTIs

Parenteral DTIs are presently approved for use in patients with active HIT and those with a previous history of HIT who require anticoagulation therapy.

Consultation with a hematologist or anticoagulation expert is recommended when using these new anticoagulant drugs because of both drug and disease complexities.

Argatroban

This is a small-molecular-weight reversible inhibitor of the active site of thrombin (univalent). This agent is excreted normally in patients with renal insufficiency, but the dose must be reduced in patients with hepatic impairment.

Bivalirudin

This is a semisynthetic bivalent inhibitor of thrombin. However, unlike hirudin, bivalirudin produces only transient reversal of thrombin and a shorter half-life of 25 minutes. It has minimal renal excretion.

Lepirudin (recombinant hirudin)

Note that on April 1, 2012, lepirudin was removed from the European market. Lepirudin will no longer be manufactured after May 2013.

This is a potent specific inhibitor of thrombin that forms a slowly reversible complex with the enzyme by binding to both its active site and an exosite focus (bivalent effect). It is cleared predominantly by the kidneys with a half-life of 40 minutes post-IV dose and 120 minutes post-subcutaneous dose. It has almost irreversible binding to thrombin and has been associated with an increased risk of major bleeds in one study.

4.1b. Adverse Effects, Parenteral DTI

- Hemorrhage
- Patients with repeat courses of lepirudin may require more frequent monitoring due to antibody formation

4.2b. Contraindications, Parenteral DTI

- Active major bleeding
- Hypersensitivity to hirudin, lepirudin, bivalirudin, argatroban

4.3b. Precautions, Parenteral DTI

- Severe hypertension
- History of recent major surgery
- History of recent major bleeding
- History of recent cerebrovascular accident

- Liver dysfunction (argatroban)
- Renal dysfunction (lepirudin) (lepirudin will no longer be manufactured after May 2013)
- Gastrointestinal ulceration
- Patients with repeat courses of lepirudin may require more frequent monitoring due to antibody formation
- Rare case reports of anaphylaxis with reexposure to lepirudin

4.4b. Pregnancy, Parenteral DTI

- FDA Pregnancy Category B *[R]*

4.5b. Breastfeeding, Parenteral DTI

- Likely compatible, no human data *[R]*

4.6b. Dosing, Parenteral DTI

Testing should be obtained before initiation of direct thrombin inhibitors:

- CBC/platelet count
- INR
- aPTT
- Liver enzymes (ALT, AST, GGT)
- Creatinine

Table: Treatment Options for HIT (With or Without Thrombosis)

Argatroban	Bivalirudin	Lepirudin
• Dose adjustment is necessary in patients with hepatic impairment. • Patients with heart failure, multiple organ system failure and anasarca, as well as those in the immediate post-cardiac surgery period, should receive a lower initial infusion rate *[R]*. • Dose adjusted to maintain aPTT at 1.5-3.0 times normal (not to exceed 100 seconds).	• Dose adjustment is necessary in patients with renal impairment. • Dose adjusted to maintain aPTT at 1.5-2.5 times normal	• No longer manufactured after May 2013. • Dose adjustment is necessary in patients with renal impairment. • There are two dosing regimens available: the FDA-approved dose and an alternate dose recommended by the CHEST guidelines *[R]*. The alternate dosing regimen has been recommended due to higher rates of bleeding associated with the FDA-approved dosing. • The alternate dosing regimen recommends omitting the initial IV bolus unless there is perceived life- or limb-threatening thrombosis, where a reduced bolus dose is preferred *[R]*. • Dose adjusted to maintain aPTT at 1.5-2.5 times normal.

aPTT, activated partial thromboplastin time; FDA, U.S. Food and Drug Administration

4.7b. Monitoring, Parenteral DTI

- The aPTT testing is commonly used to monitor DTIs. However, different aPTT reagents show variable sensitivity to the effects of the DTIs. The response of the aPTT test can plateau as the level of the DTI increases. Therefore, the aPTT does not accurately reflect the increasing concentration of DTI in the patient *[NA]*.
- The ecarin clotting time has been shown to be a superior test for monitoring recombinant hirudin and argatroban therapy. However, this test is not yet widely available in clinical laboratories.
- The DTIs prolong the INR. Among DTIs, argatroban causes the greatest amount of prolongation of this test. Interpretation of the INR during the transition from argatroban to warfarin is difficult. The package insert for argatroban describes one method of assessing the adequacy of warfarin anticoagulation during this transition. However, this method requires discontinuation of argatroban anticoagulation to assess the degree of INR prolongation due to warfarin. If the patient has not achieved adequate anticoagulation with warfarin, there is risk of further thrombosis. A second method utilizes chromogenic factor X testing. This method allows the patient to remain on argatroban anticoagulation while warfarin therapy is initiated. Factor X levels are decreased by warfarin, but are unaffected by argatroban. Previous studies have demonstrated that a chromogenic factor X level of 45% corresponds to an INR of >2 *[B]*. Therefore, chromogenic factor X levels can be obtained daily during the transition period. Once the factor X level is less than

45%, the argatroban can be stopped. A confirmatory INR should be performed once the argatroban has been cleared and before the next warfarin dose. A specific target chromogenic factor X level corresponding to an INR of 2 can be determined by each coagulation laboratory.

4.8b. Correction of Supratherapeutic Anticoagulation/Reversal, Parenteral DTI

The major side effect of DTIs is bleeding. There is no antidote for these medications should bleeding occur, which further supports the use of agents with a short half-life *[R]*.

4.9b. Patient Education, Parenteral DTI

Importance of understanding aPTT and target ranges

Know and watch for signs of bleeding.

5. Oral Direct Factor Xa Inhibitors

5.0. Key Considerations for Rivaroxaban

Rivaroxaban is an oral direct factor Xa inhibitor that selectively blocks the active site of factor Xa. Rivaroxaban does not require a cofactor (such as anti-thrombin) for activity.

Rivaroxaban 10 mg tablets may be taken without regard to food.

Based on pharmacokinetic data, food improves bioavailability of the 15 mg and 20 mg tablets; therefore, rivaroxaban 15 and 20 mg doses should be taken with food.

The maximum concentration of rivaroxaban occurs within 2 to 4 hours of administration. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects.

- Rivaroxaban is FDA approved for prevention of DVT and pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery, treatment of DVT and PE, reduction in the risk of recurrence of DVT and PE, and non-valvular atrial fibrillation for stroke prevention.
- Like warfarin and dabigatran, it requires the same careful risk/benefit assessment for patients at great risk for hemorrhage.
- Avoid use of rivaroxaban for treatment of DVT and PT, reduction of risk of recurrence of DVT and PE, and prevention of DVT and PE in patients undergoing knee or hip replacement surgery with a creatinine clearance (CrCl) <30 mL/min.
- Avoid use of rivaroxaban in patients with non-valvular atrial fibrillation and a creatinine clearance (CrCl) <15 mL/min.
- Prior to procedures, the rivaroxaban must be held at least 24 hours. Longer times may be considered for patients with renal impairment, having major surgery and/or spinal puncture.
- An increased rate of stroke has been observed during transition from rivaroxaban to warfarin in patients with non-valvular atrial fibrillation. If rivaroxaban must be stopped for a reason other than bleeding, consider administering another anticoagulant.
- No antidote is available.

5.1. Adverse Effects, Rivaroxaban

Most common adverse reactions with rivaroxaban are bleeding complications.

Table 10 in the original guideline document shows the number of patients in the ROCKET AF trial experiencing various types of bleeding.

5.2. Contraindications, Rivaroxaban

Patients with prohibitive bleed risks were not included in studies of rivaroxaban. As with all anticoagulants, extreme caution should be used in giving rivaroxaban to patients with bleeding diatheses, fall risks, alcohol abuse or compliance issues. An individual patient's risk of thrombosis versus risk of bleeding needs to be assessed before use of this or any anticoagulant.

Pregnant patients and those with valvular heart disease have not been studied and are not candidates for this drug.

Dose adjustment or avoidance of rivaroxaban should be considered in patients with severe renal insufficiency, especially if the patient's kidney function is in flux.

Moderate (Child-Pugh B) and severe hepatic (Child-Pugh C) impairment or with any hepatic disease associated with coagulopathy.

5.3. Precautions, Rivaroxaban

An increased rate of stroke was observed in the ROCKET AF trial during transition from rivaroxaban to warfarin in patients with non-valvular atrial fibrillation. If rivaroxaban must be stopped for a reason other than bleeding, consider administering another anticoagulant *[A]*.

Drug Interactions

Drug-Drug Interactions

Rivaroxaban is a substrate of CYP3A4/5 and p-glycoprotein (P-gp). Inhibitors and inducers of these CYP450 enzymes or transporter may result in changes in rivaroxaban exposures.

Drugs that are combined P-gp and CYP3A4 inhibitors increase rivaroxaban concentration (e.g., ketoconazole, ritonavir, clarithromycin, erythromycin, fluconazole). It is recommended to avoid concomitant administration of rivaroxaban with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin).

Drugs that are combined P-gp and strong CYP3A4 inducers decrease rivaroxaban concentration. It is recommended to avoid concomitant administration of rivaroxaban with P-gp and strong CYP3A4 inducers (e.g., rifampin).

Use of other anticoagulants, antiplatelets, NSAIDs or aspirin increase the risk of bleeding. Aspirin monotherapy (less than 100 mg) and thienopyridine monotherapy were allowed in ROCKET AF trial. Only 34.9% of rivaroxaban patients took aspirin (less than 100 mg) sometime during trial. Thienopyridine use was not reported in the trial *[A]*.

Drug-Disease Interactions

Patients with renal impairment receiving full dose rivaroxaban concomitantly with drugs that are combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, azithromycin, diltiazem, dronedarone, verapamil) may have significant increases in rivaroxaban concentration.

5.4. Pregnancy, Rivaroxaban

Pregnancy category C. There are no adequate or well-controlled studies of rivaroxaban in pregnant women, and dosing for pregnant women has not been established.

Pregnant patients are not candidates for this drug.

5.5. Breastfeeding, Rivaroxaban

It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted in the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue rivaroxaban, taking into account the importance of the drug to the mother.

5.6. Dosing, Rivaroxaban

DVT/PE Prophylaxis in Hip/Knee Replacement Dosing

The FDA-approved dosing of rivaroxaban for prevention of DVT/PE in patients undergoing hip or knee replacement is 10 mg once daily with or without food. Avoid use in patients with a creatinine clearance (CrCl) <30 mL/min. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has occurred.

For patients undergoing:

- Hip replacement: treatment duration of 35 days is recommended
- Knee replacement: treatment duration of 12 days is recommended

DVT and PE Treatment and Reduction in the Risk of Recurrence of DVT and PE Dosing

The FDA approved dose is 15 mg twice a day for the first 21 days for the initial treatment of acute DVT or PE. After the initial treatment period, the dose is 20 mg once daily for the rest of the treatment period for the long-term reduction in the risk of recurrence of DVT or PE. Avoid use in patients with a CrCl < 30 mL/min.

Non-Valvular Atrial Fibrillation Dosing

The FDA-approved dosing of rivaroxaban for use in non-valvular atrial fibrillation is 20 mg once daily with evening meals for patients with CrCl >50 mL/min. For patients with CrCl 15-50 mL/min, the recommended dose is 15 mg once daily with evening meals. Avoid use in

patients with a CrCl <15 mL/min.

Perioperative Management

If rivaroxaban must be discontinued to reduce the risk of bleeding for any type of procedure, it should be stopped at least 24 hours prior to the procedure. Longer times may be considered for patients with renal impairment, having major surgery and/or spinal puncture.

Rivaroxaban should be restarted after the procedure as soon as adequate hemostasis has been achieved.

5.7. Monitoring and Effect on Laboratory Testing, Rivaroxaban

Routine monitoring of rivaroxaban is not needed. In some clinical situations, evaluation of rivaroxaban effect would be helpful. These situations include rivaroxaban-treated patients presenting with thrombosis or hemorrhage, possible overdose, evaluation of compliance and assessment of rivaroxaban effect prior to surgery. A chromogenic Xa assay using rivaroxaban calibrators and controls would be helpful in this assessment; however, this assay is not yet available in the routine coagulation laboratory *[C]*.

Rivaroxaban prolongs the PT as well as the aPTT at near peak levels 2 hours after drug administration. This prolongation is not seen 12 hours after the dose is given. The degree of prolongation is dependent on the reagents used for the assays. The TT is not affected by rivaroxaban. Fibrinogen levels using the Clauss method are not affected by rivaroxaban. However, fibrinogen measurements using an assay derived from the PT assay are prolonged 2 hours after drug administration. This prolongation is variable and dependent on the reagents used for the test *[C]*.

5.8. Correction of Supratherapeutic Anticoagulation/Reversal, Rivaroxaban

Note: Consensus-based statements comprise the content of this section on rivaroxaban. It is important to note that, at the time of writing, there was little data to support these consensus-based recommendations.

There are limited options for management of bleeding on rivaroxaban as there is no antidote for reversal of the anticoagulation effect of the drug.

If rivaroxaban was consumed within 2 hours of presentation, activated charcoal, at standard doses, should be considered.

Rivaroxaban is highly protein bound and is not expected to be dialyzable.

FFP infusion will not reverse the anticoagulation effect of rivaroxaban, as the drug will inhibit factor X in the transfused plasma. (It is important to note that the prolonged clotting times on rivaroxaban are a reflection of factor X inhibition and not a clotting factor deficiency.)

As a last resort, one could consider use of procoagulant hemostatic agents such as rFVIIa, activated or non-activated PCCs. In healthy subjects, the anticoagulant effect of rivaroxaban could be reversed with administration of a non-activated PCC *[A]*.

The ICSI work group has included rFVIIa or PCC as options to help with clot formation at the site of bleeding. They do not reverse the drug, the correct dose is unknown, and there is no FDA approval for this use. Thrombosis is a known side effect of rFVIIa and PCC.

Protocol for Management of Bleeding on Rivaroxaban

Consensus-Based Protocol for Bleeding Management

Note:

> - Primary use would be in the emergency room and hospital settings where adult patients on rivaroxaban are bleeding.
> - Consensus-based statements comprise the content of this section on rivaroxaban. It is important to note that, at the time of writing, there was little data to support these consensus-based recommendations.

- There is no specific agent to reverse the drug.
- Plasma will not reverse the drug as rivaroxaban will inhibit factor X in transfused plasma.
- There is very little data to help guide us in managing bleeding complications on the drug.

Note:

> - The PTT and INR may be abnormal on rivaroxaban.
> - Clotting times do not accurately reflect drug levels.

For minor bleeding:

- Evaluate drug compliance, change in renal function, whether anatomical defects explain hemorrhage.
- Use local measures to control the bleeding.
- Keep hydrated.
- Replace fluids and blood products as needed.
- Clinical judgment to hold or continue rivaroxaban. Stopping the drug will decrease the bleeding risk, but may increase risk of stroke. Weigh the risk of stroke and the severity of the bleeding. Consider additional factors, such as duration of the drug effects and the onset of action when restarting (peak activity within two to four hours).

For severe or life-threatening bleeding:

- Stop rivaroxaban.
- Lab testing
  - CBC, platelet count, LFT, aPTT, INR, TT, creatinine and fibrinogen activity
  - Repeat testing per institutional protocols or, at a minimum, every 4 to 6 hours until bleeding has stopped.
- Control the bleeding site and supportive care of patient.
- Contact surgery or interventional radiology for embolization.
- Administer activated charcoal if the drug has been given within 2 hours.
- Blood transfusion
  - Transfuse RBCs per institutional guidelines or to keep Hgb >8 gm/dL
  - After the 4th unit of RBCs, start giving RBCs and plasma on a 1:1 ratio (to avoid a dilutional coagulopathy).
  - Cryoprecipitate, give 10 units after the 8th unit of RBCs, 4th unit of plasma – may not need cryoprecipitate if fibrinogen activity is >100 mg/dL.
- rFVIIa or PCC could be considered if bleeding is life-threatening. They do not reverse the drug and the correct dose is unknown. Thrombosis is a potential side effect of both rFVIIa and PCC.

5.9. Patient Education, Rivaroxaban

- Instruct patient to promptly report signs/symptoms of prolonged or excessive bleeding.
- Advise patient to notify physician or dentist of medication use prior to surgical procedures.
- Tell patient not to discontinue the drug unless directed by a physician.
- Advise patient that there are multiple significant drug-drug interactions for this drug and to consult health care professional prior to any new drug use (including over-the-counter and herbal drugs) as bleeding risk may increase with certain drugs (e.g., aspirin, NSAIDs, St. John's wort).

6. Antiplatelet Agents

6.0. Introduction, Antiplatelet Agents

Platelet involvement with pathologic thrombosis and vascular occlusion in both venous and arterial systems has been a recognized target and challenge for therapeutic intervention. Antiplatelet drugs provide relatively safe and variably efficacious alternatives for reduction of excessive risk in several common clinical conditions, notably cardiac and cerebral atherothrombosis. In modern clinical practice, antiplatelet drugs play a role with other means of risk reduction in both primary and secondary prevention of vascular morbidity, and in selected acute event-management situations. There is substantial basic scientific and clinical trial data available to make rational and selective management decisions for individual patients in all conceivable settings of clinical practice.

Principles

1. Antithrombotic therapeutic benefit is relative to individual patient morbidity, tolerance, and hemorrhagic risk.
2. In general, individual patient thrombotic risk must exceed 3% per year to realize a clinically meaningful benefit from antiplatelet drugs.

6.0a. Key Considerations for Oral Antiplatelet Agents

- Aspirin
- Thienopyridines (clopidogrel, prasugrel)
- Cyclopentyltriazolopyrimidine (ticagrelor)

Drug Interaction with Proton Pump Inhibitors (PPI)

In November 2009 the FDA issued a statement advising prescribers that, in patients taking clopidogrel, to avoid using selected PPIs (and other drugs – e.g., cimetidine, esomeprazole, fluoxetine, fluconazole, ketoconazole) that inhibit CYP2C19.

Though the FDA issued a boxed warning, post-hoc analysis of two studies *[A]*, *[B]* does not confirm these adverse cardiovascular

outcomes. It has been difficult for clinicians to assimilate this information and to develop strategies for managing patients who might benefit from antiplatelet therapy, yet who might suffer from GI bleeding. In 2010, the American College of Cardiology Foundation (ACCF), the American College of Gastroenterology (ACG), and the American Heart Association (AHA) issued an expert consensus document on the concomitant use of proton pump inhibitors (PPI) and thienopyridines.

Refer to the original guideline document for a discussion of CYP2C19 gene polymorphisms and clopidogrel effect.

6.1a. Adverse Effects, Oral Antiplatelet Agents

Combination of aspirin and clopidogrel and/or combination with warfarin or other anticoagulant have been shown to increase the risk of major bleeding.

Aspirin

Hemorrhage, with underlying hemostatic defects: uremia, hemophilia, anticoagulation therapy. Hemorrhage, without defects: odds ratio (OR) 1.6 in high-risk patients *[M]*.

Gastric irritation: dose-related *[A]*

- No better with coated or buffered tablets *[D]*
- Influence of concomitant cyclooxygenase (COX)-2 inhibitors/NSAIDs
- Withhold NSAIDs for 30 minutes after taking aspirin

Thienopyridines (clopidogrel, prasugrel)

Thrombotic thrombocytopenic purpura (TTP), sometimes life-threatening, may occur, usually within 2 weeks of treatment initiation *[D]*.

Hemorrhage 9%; severe in 1% to 2%/year of chronic treatment

Thrombocytopenia

Allergic rash

Diarrhea

Dipyridamole/Aspirin

Systemic vasodilation, with secondary dizziness, syncope, myocardial ischemia

Headache

Hemorrhage is NOT a common problem

6.2a. Contraindications, Oral Antiplatelet Agents

- Major hemorrhage
- Hypersensitivity to NSAIDs (aspirin)
- Platelet count less than 50,000

6.3a. Precautions, Oral Antiplatelet Agents

- Patients at risk of increased bleeding from trauma, surgery or other pathological condition (particularly gastrointestinal and intraocular)
- Alcohol use (three or more drinks/day)
- Pregnancy (third trimester)
- Gastrointestinal symptoms, peptic ulcer disease
- Renal failure
- Severe hepatic insufficiency
- Concomitant use of more than one antithrombotic drug
- Syndrome of asthma, rhinitis and nasal polyps

6.4a. Pregnancy, Oral Antiplatelet Agents

Third-trimester risks of placental separation and hemorrhage *[A]*. FDA class D positive evidence of human fetal risk. Maternal benefit may outweigh fetal risk in serious or life-threatening situations.

6.5a. Breastfeeding, Oral Antiplatelet Agents

FDA class Possibly Unsafe: Available animal or human data demonstrates potential or actual adverse effects to infants. Consider alternatives or weigh risks and benefits. Some community practice reflects use of 81 mg aspirin (acetylsalicylic acid [ASA]) daily as antiplatelet therapy.

6.6a. Dosing, Oral Antiplatelet Agents

Aspirin

For all clinically important endpoint events, oral doses ranging between 81 and 325 mg/day are sufficient. Higher doses thought in the past to be required for clinical effects have been shown to be unnecessary, and are undesirable because of dose-related gastric and hemorrhagic side effects.

Aspirin therapy at a dose of 50 to 100 mg is recommended for patients with cryptogenic stroke and a patent foramen ovale or atrial septal aneurysm. No aspirin therapy is recommended for asymptomatic patent foramen ovale or atrial septal aneurysm.

Aspirin Resistance

Some patients at risk, as well as volunteer subjects, have shown variably submaximal responses to aspirin, as assessed by bleeding time and *in vitro* laboratory evaluations of platelet response to adenosine diphosphate (ADP) and other activating agents. Methodologic and statistical issues of sampling, and the functional limitations of available laboratory tests, are likely explanation for the failure to observe such variable dosing requirements in clinical trials.

The ultimate evidence of aspirin resistance would be occurrence of thrombosis and treatment failure, although the presumption of resistance is confounded by the many other factors promoting thrombogenesis at local tissue sites.

Dipyridamole/Aspirin

Antiplatelet oral dose containing 200 mg modified-release dipyridamole plus 25 mg aspirin. Standard-release oral dipyridamole is considered to be unreliable due to erratic absorption *[A]*.

Clopidogrel loading dose of 300 to 600 mg *[A]* results in more rapid effectiveness, but no scientifically established ideal loading schedule is available. A patient-selective phenomenon of "resistance" has been observed, as with ASA, but again no reliable laboratory test of antiplatelet effect can be recommended.

Prasugrel

Prasugrel is FDA approved for acute coronary syndrome in patients undergoing percutaneous coronary intervention (PCI). The recommended loading dose is 60 mg x1, followed by a maintenance dose of 10 mg once daily. Patients should also take concomitant aspirin 75 to 325 mg once daily.

Prasugrel has an FDA black box warning regarding bleeding risk, and patient selection is important.

Candidates for prasugrel should meet the following criteria:

- Acute coronary syndrome managed by PCI
- Receiving adjunct aspirin therapy
- Not undergoing coronary artery bypass graft (CABG)
- <75 years old
- Weight ≥60 kg
- No history of transient ischemic attack (TIA)/stroke or bleeding predisposition

[A]

Ticagrelor

Ticagrelor is a P2Y12 platelet inhibitor with the FDA indication to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction).

Dosage and Administration: Initiate treatment with 180 mg (two 90 mg tablets) and continue with 90 mg twice-a-day maintenance dose. After the initial loading dose of aspirin of 325 mg, use a daily maintenance dose of 75 to 100 mg, as doses greater than 100 mg reduce the effectiveness of ticagrelor. Patients who have received a loading dose of clopidogrel can be started on ticagrelor. A patient who misses a

dose of ticagrelor should take one 90 mg tablet (his/her next dose) at its scheduled time.

FDA issued a black box warning for ticagrelor regarding bleeding risk, and patient selection is important. Contraindications include history of intracranial hemorrhage, active pathological bleeding, or severe hepatic impairment, since the latter increases the risk of bleeding because of reduced synthesis of coagulation proteins. Caution should be used in patients with a gastrointestinal bleed within the past 6 months.

Drug Interactions: Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole, which increase ticagrelor blood levels. Also avoid use with potent CYP3A inducers (rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital), which substantially reduce ticagrelor blood levels and should be avoided. Doses of simvastatin and lovastatin greater than 40 mg should be avoided since ticagrelor will result in higher serum concentrations of these drugs which are metabolized by CYP3A4. Because of inhibition of the P-glycoprotein transporter, digoxin levels should be monitored with initiation of or any change in ticagrelor therapy. When possible, discontinue ticagrelor at least five days prior to any surgery.

Dyspnea was reported in 14% of patients treated with ticagrelor and in 8% of patients taking clopidogrel in the PLATO Trial. If a patient develops new, prolonged or worsened dyspnea during treatment with ticagrelor, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to ticagrelor, no specific treatment is required; the drug should be continued without interruption. Dyspnea is usually mild to moderate in intensity, often resolves during continued treatment and is self-limiting.

Combination Antiplatelet Therapy

Combined antiplatelet therapy has been used in acute coronary syndrome for some time and proven to be effective *[A]*.

In patients with atrial fibrillation, providers should carefully select use of warfarin versus aspirin (with or without clopidogrel), based on the relative risk of stroke versus the overall risk of hemorrhage using these therapies *[A]*.

Perioperative Management of Antiplatelet Agents

Patients receiving antiplatelet agents should have these agents stopped 2 to 10 days prior to a procedure:

- Clopidogrel and prasugrel 7 days prior to surgery
- Aspirin 7 to 10 days prior to surgery
- Ibuprofen 2 days prior to surgery

Patients with recent coronary stenting may have significant risk of stent thrombosis if antiplatelet therapy is interrupted. Consultation with a cardiologist is recommended to determine the best course of action in these patients *[R]*.

6.7a. Monitoring, Oral Antiplatelet Agents

In most clinical situations, monitoring of oral antiplatelet agents is not required. There are no laboratory methods that have been shown effective in monitoring antiplatelet activity in patients. In patients where the risk of bleeding is a concern, monitoring may include CBC/platelet count.

6.8a. Correction of Supratherapeutic Anticoagulation/Reversal, Oral Antiplatelet Agents

Platelet infusion if bleeding

6.9a. Patient Education, Oral Antiplatelet Agents

Importance of understanding antiplatelet agents and target ranges

Know and watch for signs of bleeding.

Restrictions for other conditions including deep vein thrombosis, stroke, or coronary artery disease. Please refer to related ICSI guidelines for more information.

Importance of adhering to prescribed regimen

6.0b. Key Considerations for Parenteral Antiplatelet Agents

Platelet Glycoprotein IIb/IIIa Antagonists

Activation of the platelet surface receptor – P2Y12/Integrin – is the final common pathway for many metabolic activators of platelet

aggregation. Agents blocking this activation include naturally occurring polypeptides (snake venoms), synthetic polypeptides and monoclonal antibodies. In addition, these agents also inhibit thrombin generation, which is likely of importance. There are interactions with ASA, clopidogrel, heparins and thrombolytics.

6.1b. Adverse Effects, Parenteral Antiplatelet Agents

Major bleeding

Thrombocytopenia (less than 5,000/microliter) less than 1% to 2%, usually asymptomatic *[M]*

6.2b. Contraindications, Parenteral Antiplatelet Agents

- Bleeding diathesis or oral anticoagulant use within 7 days
- History of vasculitis
- Intracranial tumor, arteriovenous malformation or aneurysm
- Major surgery or trauma
- Severe uncontrolled hypertension
- Thrombocytopenia
- Active or recent internal bleeding

6.3b. Precautions, Parenteral Antiplatelet Agents

- Concomitant administration with thrombolytics, oral anticoagulants, NSAIDs, dipyridamole and other antiplatelet drugs increase the risk of bleeding.
- A low-dose, weight-adjusted heparin regimen is recommended to minimize the risk of bleeding.
- Minimize arterial and venous punctures, intramuscular (IM) injections and use of urinary catheters, nasotracheal intubation, nasogastric tubes and automatic blood pressure cuffs.
- Arterial sheath should not be removed unless aPTT is 50 seconds or less, OR the ACT is 175 seconds or less, and heparin has been discontinued for at least 2 hours.
- Full-dose heparin should be stopped at least 2 hours before femoral artery sheath removal and adequate hemostasis are achieved.
- Patients should be maintained on adequate bed rest following sheath removal or discontinuation of IIB/IIIA inhibitors.
- Thrombocytopenia has been observed; platelet counts should be monitored.

6.4b. Pregnancy, Parenteral Antiplatelet Agents

Little information is known, and not all platelet glycoprotein antagonist drugs have been studied. All studies to date have been animal studies.

6.5b. Breastfeeding, Parenteral Antiplatelet Agents

Little information is known, but it does not appear that parenteral antiplatelet drugs are excreted in breast milk.

6.6b. Dosing, Parenteral Antiplatelet Agents

Abciximab

IV bolus 0.25 mg/kg plus 0.125 microgram/kg/min infusion; effective in 80% or more in PCI subjects

Half-life at 30 minutes; 65% attachment to platelet surface

Peak effects at 2 hours: receptor blockade, aggregation, bleeding time

Recovery over 12 to 48 hours

Tirofiban

IV bolus 0.4 microgram/kg/min x 30 min, then 0.1 microgram/kg/min

Renal clearance issues (less than 30 mL/min)

Eptifibatide

IV bolus 180 microgram/kg, infusion 2 microgram/kg/min

Return to normal variable, usually within one hour of discontinuation of infusion.

Neuraxial Blockade Management (Spinal/Epidural)

Please see the NGC summary of the ICSI guideline Venous Thromboembolism Prophylaxis.

6.7b. Monitoring and Effect on Laboratory Testing, Parenteral Antiplatelet Agents

In most clinical situations, monitoring of oral antiplatelet agents is not required. There are no laboratory methods that have been shown effective in monitoring antiplatelet activity in patients. In patients where the risk of bleeding is a concern, monitoring may include CBC/platelet count.

6.8b. Treatment of Bleeding/Reversal, Parenteral Antiplatelet Agents

Platelet infusion if bleeding

6.9b. Patient Education, Parenteral Antiplatelet Agents

If a patient is to receive bridging therapy, the patient or a caregiver must show proficiency in the injection technique and proficiency with adhering to the perioperative schedule.

Definitions:

Classes of Research Reports

Class	Description
Primary Reports of New Data Collections	
A	Randomized, controlled trial
B	Cohort-study
C	Nonrandomized trial with concurrent or historical controls • Case-control study • Study of sensitivity and specificity of a diagnostic test • Population-based descriptive study
D	Cross-sectional study • Case series • Case report
Reports That Synthesize or Reflect upon Collections of Primary Reports	
M	Meta-analysis • Systematic review • Decision analysis • Cost-effectiveness analysis
R	Consensus statement • Consensus report • Narrative review
X	Medical opinion

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Conditions that require anticoagulation therapy (e.g., thrombosis)
- Conditions that may result from anticoagulation therapy (e.g., bleeding)

Guideline Category

Management

Prevention

Risk Assessment

Clinical Specialty

Cardiology

Emergency Medicine

Family Practice

Hematology

Internal Medicine

Neurology

Pharmacology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Health Plans

Hospitals

Managed Care Organizations

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

- To help physicians make risk-benefit treatment decisions
- To serve as a tool to use for patients treated with antithrombotics

- To bring about consistency in recommendations that are common to the scope of related Institute for Clinical Systems Improvement (ICSI) cardiovascular guidelines

Target Population

Any adult patient receiving anticoagulation therapy

Note: Please refer to related Institute for Clinical Systems Improvement (ICSI) guidelines for specific target populations.

Interventions and Practices Considered

1. Warfarin
2. Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH)
3. Synthetic pentasaccharide (fondaparinux)
4. Direct thrombin inhibitors (e.g., dabigatran)
5. Oral direct factor Xa inhibitors (e.g., rivaroxaban)
6. Antiplatelet agents, including oral and parenteral

Major Outcomes Considered

- Risk and incidence of adverse effects of anticoagulation (e.g., major bleeding, skin necrosis, heparin induced thrombocytopenia)
- Therapeutic anticoagulation levels (e.g., international normalized ratio [INR])

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A consistent and defined process is used for literature search and review for the development and revision of Institute for Clinical Systems Improvement (ICSI) guidelines. Literature search terms for the current revision included a search of clinical trials, meta-analyses, and systematic reviews restricted to human studies and English language in the following areas: fondaparinux/antagonists and inhibitors; anticoagulants factor Xa inhibitor/antagonists and inhibitors; platelet glycoprotein GPIIb-IIIa; chromogenic factor X inhibitor; platelet aggregation/drug effects; platelet aggregation inhibitors; ticagrelor; argatroban; dabigatran; rivaroxaban, apixaban, edoxaban, otamixaban; antithrombins; pregnancy; direct thrombin inhibitors; CYP2C19; metabolizer; clopidogrel and Plavix®; ticlopidine/analogs and derivatives. Included publications are from PubMed from April 2010 to November 2011. Included are human data, English language.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Classes of Research Reports

Class	Description
Primary Reports of New Data Collections	
A	Randomized, controlled trial
B	Cohort-study
C	Nonrandomized trial with concurrent or historical controls • Case-control study • Study of sensitivity and specificity of a diagnostic test • Population-based descriptive study
D	Cross-sectional study • Case series • Case report
Reports That Synthesize or Reflect upon Collections of Primary Reports	
M	Meta-analysis • Systematic review • Decision analysis • Cost-effectiveness analysis
R	Consensus statement • Consensus report • Narrative review
X	Medical opinion

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Development Process

A work group consisting of 6 to 12 members that includes physicians, nurses, pharmacists, other healthcare professionals relevant to the topic, and

an Institute for Clinical Systems Improvement (ICSI) staff facilitator develops each document. Ordinarily, one of the physicians will be the leader. Most work group members are recruited from ICSI member organizations, but if there is expertise not represented by ICSI members, 1 or 2 work group members may be recruited from medical groups, hospitals or other organizations that are not members of ICSI. Patients on occasion are invited to serve on work groups.

The work group will meet for 7 to 8 three-hour meetings to develop the guideline. A literature search and review is performed and the work group members, under the coordination of the ICSI staff facilitator, develop the algorithm and write the annotations and literature citations.

Once the final draft copy of the guideline is developed, the guideline goes to the ICSI members for critical review.

Revision Process of Existing Guidelines

ICSI scientific documents are revised every 12 to 24 months as indicated by changes in clinical practice and literature. For documents that are revised on a 24-month schedule, ICSI checks with the work group on an annual basis to determine if there have been changes in the literature significant enough to cause the document to be revised earlier or later than scheduled. For yearly reviewed documents, ICSI checks with every work group 6 months before the scheduled revision to determine if there have been changes in the literature significant enough to cause the document to be revised earlier than scheduled.

Literature Search

ICSI staff, working with the work group to identify any new pertinent clinical trials, systematic reviews, or regulatory statements and other professional guidelines, conduct a literature search.

Revision

The work group will meet for 1 to 2 three-hour meetings to review the literature, respond to member organization comments, and revise the document as appropriate.

A second review by members is indicated if there are changes or additions to the document that would be unfamiliar or unacceptable to member organizations. If a review by members is not needed, the document goes to the appropriate steering committee for approval according to the criteria outlined in the "Description of Method of Guideline Validation" field.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Critical Review Process

The purpose of Critical Review is to provide an opportunity for the clinicians in the member groups to review the science behind the recommendations and focus on the content of the guideline. Critical review also provides an opportunity for clinicians in each group to come to consensus on feedback they wish to give the work group and to consider changes needed across systems in their organization to implement the guideline.

All member organizations are expected to respond to critical review guidelines. Critical review of guidelines is a criterion for continued membership within the Institute for Clinical Systems Improvement (ICSI).

After the critical review period, the guideline work group reconvenes to review the comments and make changes as appropriate. The work group prepares a written response to all comments.

Document Approval

Each document is approved by the Committee for Evidence-Based Practice (CEBP).

The committee will review and approve each guideline/protocol, based on the following criteria:

- The aim(s) of the document is clearly and specifically described.
- The need for and importance of the document is clearly stated.
- The work group included individuals from all relevant professional groups and had the needed expertise.
- Patient views and preferences were sought and included.
- The work group has responded to all feedback and criticisms reasonably.
- Potential conflicts of interest were disclosed and do not detract from the quality of the document.
- Systematic methods were used to search for the evidence to assure completeness and currency.
- Health benefits, side effects, risks and patient preferences have been considered in formulating recommendations.
- The link between the recommendation and supporting evidence is clear.
- Where the evidence has not been well established, recommendations based on community practice or expert opinion are clearly identified.
- Recommendations are specific and unambiguous.
- Different options for clinical management are clearly presented.
- Clinical highlights and recommendations are easily identifiable.
- Implementation recommendations identify key strategies for *health care systems* to support implementation of the document.
- The document is supported with practical and useful tools to ease *clinician* implementation.
- Where local resource availability may vary, alternative recommendations are clear.
- Suggested measures are clear and useful for quality/process improvement efforts.

Once the document has been approved, it is posted on the ICSI Web site and released to members for use.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is classified for selected recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate risk-benefit treatment decisions regarding anticoagulation therapy and appropriately managed patients on anticoagulation therapy to maximize safety and efficacy

Potential Harms

- The major side effect of antithrombotic drugs is bleeding either from supratherapeutic effect or by accentuating the blood loss of patients with an existing source of bleeding.
- Recent concerns about concomitant use of proton pump inhibitors (PPIs) and *clopidogrel* ought to be addressed on a patient-by-patient basis with discontinuation of PPI if there is no definite indication for its use.
- Anaphylaxis occurs in 1% of patients who have previously received protamine. Other adverse effects of protamine include hypotension.
- Vitamin K can lead to warfarin resistance and subsequently, to an increased risk of thromboembolism.

Refer to the "Major Recommendations" field for information on drug interactions, adverse effects, precautions, and antithrombotic drug use in

pregnancy and breastfeeding.

Contraindications

Contraindications

- There are few absolute contraindications to antithrombotic therapy with the exception of active life-threatening bleeding. The decision to treat a patient with antithrombotic drugs takes into account an individual patient's risk for thrombosis if not treated weighed against the risk of bleeding while on antithrombotic drug therapy.
- Patients suspected of having any form of heparin-induced thrombocytopenia (HIT) should have their heparin stopped while antibody testing for HIT is performed.

Refer to Annotations #1.2, 2.2, 3.2, 4.2a, 4.2b, 5.2, 6.2a, and 6.2b in the "Major Recommendations" section for relative contraindications to antithrombotic therapy.

Qualifying Statements

Qualifying Statements

- The information contained in this Institute for Clinical Systems Improvement (ICSI) Health Care Guideline is intended primarily for health professionals and other expert audiences.
- This ICSI Health Care Guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients and families are urged to consult a health care professional regarding their own situation and any specific medical questions they may have. In addition, they should seek assistance from a health care professional in interpreting this ICSI Health Care Guideline and applying it in their individual case.
- This ICSI Health Care Guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition.

Implementation of the Guideline

Description of Implementation Strategy

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experience and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

Implementation Tools

Quick Reference Guides/Physician Guides

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Maddali S, Biring T, Bluhm J, Kopecky S, Krueger K, Larson T, Mikelson M, Miley T, Morton C, Pruthi R, Schullo-Feulner A. Antithrombotic therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Feb. 88 p. [186 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2001 Sep (revised 2013 Feb)

Guideline Developer(s)

Institute for Clinical Systems Improvement - Nonprofit Organization

Guideline Developer Comment

The Institute for Clinical Systems Improvement (ICSI) comprises 50+ medical group and hospital members representing 9,000 physicians in Minnesota and surrounding areas, and is sponsored by five nonprofit health plans. For a list of sponsors and participating organizations, see the ICSI Web site.

Source(s) of Funding

- The Institute for Clinical Systems Improvement (ICSI) provided the funding for this guideline. The annual dues of the member medical groups and sponsoring health plans fund ICSI's work. Individuals on the work group are not paid by ICSI, but are supported by their

medical group for this work.
- ICSI facilitates and coordinates the guideline development and revision process. ICSI, member medical groups, and sponsoring health plans review and provide feedback, but do not have editorial control over the work group. All recommendations are based on the work group's independent evaluation of the evidence.

Guideline Committee

Committee on Evidence-Based Practice

Composition of Group That Authored the Guideline

Work Group Members: Seema Maddali, MD, MHA (*Work Group Co-Leader*) (HealthEast Care System) (Hospitalist); Colleen Morton, MD (*Work Group Co-Leader*) (HealthPartners Medical Group and Regions Hospital) (Hematology/Oncology); Timinder Biring, MD (HealthPartners Medical Group and Regions Hospital) (Interventional Cardiology); Kori Krueger, MD (Marshfield Clinic) (Internal Medicine); Tonja Larson, PharmD, BCPS (Marshfield Clinic) (Pharmacy); Melissa Mikelson, RN, BSN (Marshfield Clinic) (Internal Medicine); Stephen Kopecky, MD (Mayo Clinic) (Cardiology); Rajiv Pruthi, MBBS (Mayo Clinic) (Hematology); Timothy Miley, MD (Park Nicollet Health Services) (Pathology); Anne Schullo-Feulner, PharmD, BCPS (Park Nicollet Health Services) (Pharmacy); Jim Bluhm, MPH (Institute for Clinical Systems Improvement) (Team Director)

Financial Disclosures/Conflicts of Interest

The Institute for Clinical Systems Improvement (ICSI) has long had a policy of transparency in declaring potential conflicting and competing interests of all individuals who participate in the development, revision and approval of ICSI guidelines and protocols.

In 2010, the ICSI Conflict of Interest Review Committee was established by the Board of Directors to review all disclosures and make recommendations to the board when steps should be taken to mitigate potential conflicts of interest, including recommendations regarding removal of work group members. This committee has adopted the Institute of Medicine Conflict of Interest standards as outlined in the report Clinical Practice Guidelines We Can Trust (2011).

Where there are work group members with identified potential conflicts, these are disclosed and discussed at the initial work group meeting. These members are expected to recuse themselves from related discussions or authorship of related recommendations, as directed by the Conflict of Interest committee or requested by the work group.

The complete ICSI Policy regarding Conflicts of Interest is available at the ICSI Web site .

Disclosure of Potential Conflicts of Interest

Timinder Biring, MD, Work Group Member
Interventional Cardiologist, HealthPartners Medical Group & Regions Hospital
National, Regional, Local Committee Affiliations: None
Guideline-Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Stephen Kopecky, MD, Work Group Member
Cardiologist, Mayo Clinic
National, Regional, Local Committee Affiliations: Member, ICSI Committee on Evidence-Based Practice
Guideline-Related Activities: ICSI Healthy Lifestyles guideline, ICSI Lipid Management guideline and ICSI Heart Failure in Adults guideline
Research Grants: None
Financial/Non-Financial Conflicts of Interest: Consultant work for Applied Clinical Intelligence and for Prime Therapeutics

Kori Krueger, MD, Work Group Member
Internal Medicine, Director of Anticoagulation Services and Quality Improvement, Marshfield Clinic
National, Regional, Local Committee Affiliations: None
Guideline-Related Activities: ICSI Lipid Management guideline

Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Tonja Larson, PharmD, BCPS, Work Group Member
Clinical Pharmacist, Marshfield Clinic
National, Regional, Local Committee Affiliations: None
Guideline-Related Activities: ICSI Diagnosis and Management of Chest Pain and Acute Coronary Syndrome (ACS) guideline and ICSI Venous Thromboembolism Prophylaxis guideline
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Seema Maddali, MD, MHA, Work Group Co-Leader
Hospitalist Medical Director, Hospitalist Medicine Service, HealthEast Care System
National, Regional, Local Committee Affiliations: None
Guideline-Related Activities: ICSI Venous Thromboembolism Diagnosis and Treatment guideline
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Melissa Mikelson, RN, BSN, Work Group Member
Internal Medicine, Manager, Care Management, Marshfield Clinic
National, Regional, Local Committee Affiliations: None
Guideline-Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Timothy Miley, MD, Work Group Member
Pathology and Laboratory Medicine, Park Nicollet Health Services
National, Regional, Local Committee Affiliations: American Society of Clinical Pathology, American Society of Hematology for work on the Practice Committee
Guideline-Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Colleen Morton, MD, Work Group Co-Leader
Hematology/Oncology, HealthPartners Medical Group & Regions Hospital
National, Regional, Local Committee Affiliations: None
Guideline-Related Activities: ICSI Consensus-Based Statement on Emergency Care of Bleeding and ICSI Venous Thromboembolism Prophylaxis guideline
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Rajiv Pruthi, MBBS, Work Group Member
Hematology, Mayo Clinic
National, Regional, Local Committee Affiliations: None
Guideline-Related Activities: ICSI Consensus-Based Statement on Emergency Care of Bleeding and ICSI Venous Thromboembolism Prophylaxis guideline
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Anne Schullo-Feulner, PharmD, BCPS, Work Group Member
Clinical Pharmacist, Park Nicollet Health Services
National, Regional, Local Committee Affiliations: None
Guideline-Related Activities: None
Research Grants: None
Financial/Non-Financial Conflicts of Interest: None

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Maddali S, Morton C, Biring T, Bluhm J, Hanson M, Kopecky S, Krueger K, Larson T, Mikelson M, Miley T, Pruthi R, Schullo-Feulner A. Antithrombotic therapy supplement. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2012 May. 87 p.

Guideline Availability

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site .

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org ; e-mail: icsi.info@icsi.org.

Availability of Companion Documents

The following is available:

- Antithrombotic therapy supplement. Executive summary. Bloomington (MN): Institute for Clinical Systems Improvement; 2013 Feb. Electronic copies: Available in Portable Document Format (PDF) from the Institute for Clinical Systems Improvement (ICSI) Web site .

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org ; e-mail: icsi.info@icsi.org.

In addition, factors for risk stratification are available in the appendices to the original guideline document .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on August 26, 2002. The information was verified by the guideline developer on September 23, 2002. This summary was updated by ECRI on May 7, 2004, July 14, 2005, and on May 17, 2006. This summary was updated by ECRI on March 6, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin sodium). This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on September 7, 2007 following the revised U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin). This NGC summary was updated by ECRI Institute on November 28, 2007. This summary was updated by ECRI Institute on March 14, 2008 following the updated FDA advisory on heparin sodium injection. This summary was updated by ECRI Institute on December 26, 2008 following the FDA advisory on Innohep (tinzaparin). This summary was updated by ECRI Institute on December 17, 2009. This summary was updated by ECRI Institute on July 27, 2010 following the FDA drug safety communication on Heparin. This summary was updated by ECRI Institute on October 19, 2010 and July 13, 2011. This NGC summary was updated by ECRI Institute on August 3, 2012. This summary was updated by ECRI Institute on January 23, 2013 following the U.S. Food and Drug Administration advisory on Pradaxa (dabigatran etexilate mesylate). This NGC summary was updated by ECRI Institute on June 10, 2013. This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

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